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(54) Title: POLYMER SURFACE COATINGS

(57) Abstract

New polymers formed from ethylenically unsaturated monomers having pendant zwitterionic groups and pendant urethane units are used to increase the biocompatibility, especially hemocompatibility, of polymeric, especially polyurethane, substrates. The polymers may either be coated onto a polymeric substrate or may be blended with a base polymer and subsequently shaped. A specific polymer is a copolymer of 2-(methacryloyloxy)ethyl)-2-(trimethylammonium) ethyl phosphate inner salt copolymerised with alkyloxy carbonylaminoethyl-methacrylate, and optionally with alkyl(meth)acrylate termonomer. The polymer is coated onto polyurethane membrane, for instance from a solution in an alcohol solvent and shows reduced blood platelet deposit compared to uncoated membranes.

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POLYMER SURFACE COATINGS

The present invention relates to new polymers, processes for producing them and processes for coating surfaces with them. The invention also provides certain new monomers used to obtain the polymers and processes for their production. The polymers are useful for coating surfaces of devices and materials which come into contact with protein-containing solutions and biological fluids, and rendering the surfaces bio- and haemocompatible. Surfaces may thus be rendered suitable for prolonged contact with living tissues and body fluids and with protein-containing solutions.

Materials used in the manufacture of separation substrates and devices, blood contacting devices contact and intraocular lenses, and other devices which are used in contact with protein-containing or biological fluids must be selected on the basis of acceptable physical and mechanical properties and compatibility with the protein-containing or biological fluid. For any given application of these materials it is usually difficult to optimise all of these considerations simultaneously and a compromise must be reached often resulting in less than optimal performance. For example, major biological problems are often encountered with materials which have otherwise optimal mechanical and physical properties. These problems often manifest themselves as undesirable deposition of biological components and in particular proteinaceous material. This protein adsorption results in blood clot formation in blood-contacting materials, the adsorption of tear components onto contact lenses resulting in deposit formation, formation of deposits on intraocular lenses and in separation media it results in blockage and failure of separation devices. Such effects lead to significant loss in operational performance and often complete rejection and failure of devices.

In the case of medical devices, for example prostheses and components of blood dialysis equipment, it is common

practice to employ biocompatible polymers to form at least the surface of the devices to discourage protein adsorption. However, these materials are not perfect and reaction with the living tissues still remain a problem; for example surface-induced thrombosis is still a major difficulty, particularly where large quantities of blood are contacted with a foreign surface such as in artificial lungs and kidneys. Formation of a clot in an artificial organ has a number of adverse or even catastrophic effects including occlusion of the blood pathway in the extracorporeal system, or embolism if the clot breaks off the artificial surface and lodges in a host blood vessel. Dialysis membranes, heart valves, circulatory-assist devices, blood substitutes and artificial lungs all share this problem.

It is known that materials for use as biocompatible coatings should ideally:

(a) be capable of reproducible manufacture as pure materials;
(b) be capable of being coated onto surfaces without being degraded or adversely changed;
(c) have the requisite mechanical and permeability properties required for the specific function of the device for which they are intended;
(d) be sterilisable without adverse changes in, for example, permeability and mechanical or surface properties;
(e) not be damaged or degraded by the biological environment;
(f) not be carcinogenic.

In applications involving direct contact with blood further restrictions exist. Materials should not:

(g) induce significant platelet adhesion;
(h) interfere with the normal clotting mechanism; or
(i) cause any significant damage to the cellular elements or soluble components of the blood.

There have been many attempts to prepare biocompatible, and specifically blood compatible (i.e, haemocompatible), surfaces, which do not activate the blood coagulation process and do not promote thrombus formation. Examples of such attempts include the preparation of negatively charged surfaces, such as by use of anionic polymers or suitably oriented electret polymers, preparation of surfaces coated with the natural anticoagulant heparin or synthetic heparin analogues, preparation of surfaces with inherently low surface free energy such as by use of silicone rubber, preparation of albumin-coated surfaces, and preparation of surfaces coated with compounds such as some polymethanes which are thought to adsorb albumin preferentially from blood. All of these however have had limitations.

Our earlier patent application, WO-A-93/01221 discloses film-forming polymers which can be used to provide stable coatings on a wide variety of surfaces including polyethylene, PVC, steel and poly(imide). The polymers contain zwitterionic groups which mimic the zwitterionic structure of phospholipids such as phosphatidylcholine and sphingomyelin which are the major components of the outer membrane of all living cells and seek to provide a biocompatible surface on a coated substrate at which the deposition of proteins and cells at the substrate is minimised when the coated substrate comes into contact with a protein-containing solution or biological fluid. The polymers also contain groups which provide stable binding of the polymer to a substrate by physisorption, covalent bonding or ionic bonding.

We have also found that compounds containing phosphoryl choline groups can reduce the adhesion or growth of microorganisms such as bacteria, yeast, algae and fungi, and, in particular bacteria, at a surface. This renders the use of copolymers containing such groups advantageous in a wide variety of situations where the growth of such microorganisms is undesirable. These include industrial

and domestic use as well as in the biomedical field wherever it is designed to reduce adhesion of bacteria to a surface.

We have now devised new film-forming polymers which are particularly suitable to provide stable coatings of polyurethane substrates. The polymers comprise zwitterionic groups intended to provide a biocompatible coating and groups containing a polyurethane-like chain which are capable of providing stable binding by physisorption to a polyurethane. Such polymers adhere to a polyurethane substrate surface through strong secondary valence interactions, i.e. through adsorption without the formation of covalent interactions.

It is also believed that when the polymers of the invention are blended with a conventional polyurethane they will provide a bulk material combining the physical and mechanical properties of the polyurethane and improved biocompatibility. The presence of pendant polyurethane-like groups in a copolymer of the invention may improve the compatibility of the copolymer for blending with a polyurethane.

In addition a variety of ligands may be attached to the polymers of the present invention when coated onto a substrate, or alternatively ligands may be attached to the polymers prior to coating on a substrate, e.g. when the polymer is in solution. The polymers of the present invention may therefore provide a means of attachment of such ligands: in such a case the polymers may comprise reactive groups capable of providing covalent bonding to a ligand. The term "ligand" includes, but is not limited to, specific binding agents such as immunoglobulins and fragments thereof, such as those useful for affinity separation and diagnostic applications, photosensitive and chemosensitive moieties, such as those useful for detector and sensor applications, and therapeutic agents useful for clinical applications. Other ligands include peptide fragments which may be chemically linked to a polymer of

the invention, such as fragments which induce cell attachment and may therefore be used to allow the polymers of the present invention to provide cell seeding.

Coatings with increased strength and stability may be produced by incorporating in the polymers residues of comonomers which contain crosslinkable groups. After coating on a substrate surface crosslinking may then be provided by subsequent reaction of such groups.

The present invention provides a polymer of one or more radical polymerisable, preferably ethylenically unsaturated, monomers, which polymer has pendant zwitterionic groups and other pendant groups containing an -NRC(O)NR- or -NRC(O)O- moiety, where the groups R are the same or different and each is hydrogen or alkyl of 1 to 4 carbon atoms, capable of stably binding the polymer by physisorption to a polymeric, usually polyurethane, substrate surface or capable of providing compatibility with base polymer, usually a polyurethane polymer, in a blend.

Such copolymers may be coated on a polymeric, preferably polyurethane, substrate surface so as to bind with good adhesion and are not removable in the environment in which the coated surfaces are used, e.g. in use as a coating on a blood-contacting surface. The polymeric substrate is formed of any plymer which can be shaped, usually by a melt-processing technique, and so is suitably a thermoplastic polymer. Any such polymeric substrate routinely used in blood contacting apparatus may be advantageously biocompatibilised using the new polymers. Such thermoplastic polymers include olefin polymers, eg ethylene polymers, vinyl chloride polymers, polycarbonates, polyesters, etc.

The polymers of the invention may be used to improve the biocompatibility of a surface. The extent to which such a polymer renders a substrate biocompatible may be assessed as a combination of factors such as reduction in the extent to which the surface causes blood platelet

activation, protein adsorption, (for instance as judged by absorption of fibrinogen from human plasma) and reaction with C-reactive protein which is caused by the presence on the surface of isolated zwitterionic, e.g. ammonium phosphate ester groups. Preferably the polymers of the invention when coated onto a substrate, provide a reduction in platelet activation of at least 70%, more preferably at least 90%, as assessed by the assay described in WO 93/01221 compared to an untreated substrate. Alternatively, the extent to which platelets are activated by adhesion to a substrate may be assessed by Scanning Election Microscopy. It is also preferred that the polymers of the invention, when coated onto a substrate, provide a reduction in fibrinogen absorption of at least 60% as assessed by the assay described in WO 93/01221 and a protein index of less than 1.5×10^{-3} compared to an untreated substrate. The protein index is defined as the ratio of the absorbency due to C-reactive protein measured in the assay described in WO 93/01221 to the reduction in fibrinogen absorption.

Polymers of the invention may also be used to reduce the tendency of microorganisms, such as bacteria, yeast, algae or fungi and in particular bacteria, to adhere to the surface. They may also be used more generally to reduce cellular adhesion at a surface. Surfaces treated with or fabricated from such polymers therefore have a wide variety of applications in the medical field such as in blood-contacting devices, and also in domestic or industrial fields wherever it is desired to reduce the adhesion of protein or microorganisms at a surface.

The nature of the pendant polyurethane-like groups in the polymers of the invention may be selected to optimise binding to a particular polymeric substrate surface which it is intended to coat with the polymer or for compatibility with a particular base polymer with which the polymer of the invention is to be blended. Thus the pendant polyurethane-like groups containing an -NRC(O)NH-

or -NRC(O)O- moiety may be matched to the structure of a particular polyurethane.

The pendant groups containing an -NRC(O)NH- or -NRC(O)O- moiety, (i.e. polyurethane-like groups) may be present in the same monomer as the zwitterionic groups or they may be in separate monomer species which are copolymerised to provide the polymer of the invention.

It will be understood that throughout, where a group is referred to as capable of binding a polymer to a surface this is intended to mean stably binding, that is, the polymer is not removed from the surface to a significant extent during the normal use thereof, usually that the polymer is not removed from the surface to a significant extent in prolonged contact with blood or other aqueous liquid.

In one embodiment the present invention therefore provides a copolymer obtained by

(i) copolymerising a radical polymerisable, preferably an ethylenically unsaturated, comonomer containing a zwitterionic group and a radical polymerisable, preferably an ethylenically unsaturated, comonomer containing a radical polymerisable moiety and a group containing an -NRC(O)NR- or NRC(O)O- moiety.

In an alternative embodiment the present invention provides a polymer obtained by

(ii) polymerising a radical polymerisable, preferably ethylenically unsaturated, monomer containing a zwitterionic group and a group containing an -NRC(O)NR- or -NRC(O)O- moiety.

The polymer may thus be a copolymer comprising residues of a radical polymerisable, preferably ethylenically unsaturated, comonomer containing a zwitterionic group and of a radical polymerisable, preferably ethylenically unsaturated comonomer containing, in addition to the radical polymerisable moiety, group containing an -NRC(O)NR- or -NRC(O)O- moiety capable of binding to a polyurethane substrate surface by

physisorption or capable of providing compatibility with a polyurethane polymer in a blend.

Alternatively such a polymer may comprise or consist of residues of a radical polymerisable, preferably ethylenically unsaturated, monomer containing a zwitterionic group and a group containing an -NRC(O)NR- or -NRC(O)O- moiety capable of binding to a polyurethane substrate surface by physisorption or capable of providing compatibility with a polyurethane polymer in a blend.

Preferably the polymer is a copolymer comprising residues of a comonomer containing such polyurethane-like group and a comonomer containing a zwitterionic group.

Optionally, the polymer may further comprise residues of one or more diluent comonomers and/or reactive comonomers to provide points of attachment for a ligand, or crosslinking.

The invention also provides a process for producing such a polymer which comprises polymerising such monomers and a process for coating a polymeric substrate surface with such a polymer, for instance a process comprising the steps of (a) polymerising such monomers to form the polymer and (b) coating the surface with the polymer so formed. Optionally, the process further comprises attaching a ligand to the polymer either in solution before coating the surface or, more preferably, when coated on the surface.

In a specific embodiment the invention further provides such polymers containing residues of a crosslinkable reactive monomer, which are uncrosslinked, when either coated on a surface or not coated on a surface and such polymers which are crosslinked when coated on a surface. The invention further provides a process of crosslinking such polymers when coated on a surface.

As yet a further feature, the present invention provides certain new monomers useful in producing the polymers of the invention, and processes for their preparation.

Monomers and comonomers which may be used in the polymers of the invention will now be described in more detail.

It is to be understood that throughout the specification (alk)acrylate, (alk)acrylic and (alk)acrylamide mean acrylate or alkacrylate, acrylic or alkacrylic and acrylamide or alkacrylamide respectively. Preferably unless otherwise stated alkacrylate, alkacrylic and alkacrylamide groups contain from 1 to 4 carbon atoms in the alkyl group thereof and are most preferably methacrylate, methacrylic or methacrylamide groups. Similarly (meth)acrylate, (meth)acrylic and (meth)acrylamide shall be understood to mean acrylate or methacrylate, acrylic or methacrylic and acrylamide or methacrylamide respectively.

Zwitterionic Monomers

The zwitterionic monomer (or comonomer) includes within its structure both a centre of permanent positive charge and also a centre of negative charge. Typically the centre of permanent positive charge is provided by a quaternary nitrogen atom and the centre of negative change is provided by a phosphate group. Preferably the zwitterionic group is an ammonium phosphate ester group such as a phosphoryl choline group or derivative thereof.

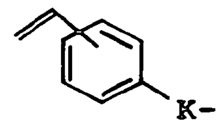
Preferred zwitterionic comonomers are of general formula (I)

$$Y-B-X \qquad (I)$$

wherein B is a straight or branched alkylene, oxaalkylene or oligo-oxaalkylene chain optionally containing one or more fluorine atoms up to and including perfluorinated chains or, if X contains a carbon-carbon chain between B and the zwitterionic group or if Y contains a terminal carbon atom bonded to B, a valence bond;

X is a zwitterionic group and

Y is an ethylenically unsaturated polymerisable group selected from

$$CH_2{=}C(R^1){-}C({=}O){-}A{-}$$ or 

wherein:

R^1 is hydrogen or a C_1-C_4 alkyl group;

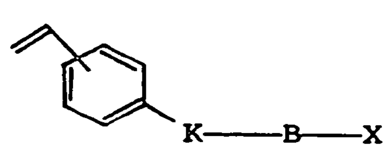
A is -O- or $-NR^2-$ where R^2 is hydrogen or a C_1-C_4 alkyl group or R^2 is -B-X where B and X are as defined above; and

K is a group $-(CH_2)_pOC(O)-$, $-(CH_2)_pC(O)O-$, $-(CH_2)_pOC(O)O-$, $-(CH_2)_pNR^3-$, $-(CH_2)_pNR^3C(O)-$, $-(CH_2)_pC(O)NR^3-$, $-(CH_2)_pNR^3C(O)O-$, $-(CH_2)_pOC(O)NR^3-$, $-(CH_2)_pNR^3C(O)NR^3-$, (in which the groups R^3 are the same or different) $-(CH_2)_pO-$, $-(CH_2)_pSO_3$ -, or, optionally in combination with B, a valence bond and p is from 1 to 12 and R^3 is hydrogen or a C_1-C_4 alkyl group.

The proviso on whether B may be a valence bond ensures that a centre of charge in the zwitterionic group X is not directly bonded to a heteroatom, such as an oxygen or nitrogen atom in Y.

Preferred zwitterionic are therefore of general formula (II) or (III).

$$CH_2{=}C(R^1){-}C({=}O){-}A{-}B{-}X \qquad \text{(II)}$$



(III)

where R^1, A, B, K and X are as defined with reference to formula (I).

Preferably in the compounds of formula (II) R^1 is hydrogen, methyl, or ethyl, more preferably methyl, so that (II) is an acrylic acid, methacrylic acid or methacrylic acid derivative.

In the compounds of formula (III) K may be a valence bond and B a group, K may be a group and B a valence bond, both K and B may be groups, or K and B may together be a valence bond. Preferably B is a group where K is a valence bond.

Where K is a group then preferably p is from 1 to 6, more preferably 1,2 or 3 and most preferably p is 1. When K is a group $-(CH_2)_pNR^3-$, $-(CH_2)_pNR^3C(O)-$, $-(CH_2)_pC(O)NR^3$, $-(CH_2)_pNR^3C(O)O-$, $-(CH_2)_pOC(O)NR^3-$ or $-(CH_2)_pNR^3C(O)NR^3-$ then R^3 is preferably hydrogen, methyl or ethyl, more preferably hydrogen.

In the compounds of formula (III) preferably the vinyl group is para to the group -K-B-X.

Preferably B is:

an alkylene group of formula $-(CR^4_2)_a-$, wherein the groups $-(CR^4_2)-$ are the same or different, and in each group $-(CR^4_2)-$ the groups R^4 are the same or different and each group R^4 is hydrogen, fluorine or C_{1-4} alkyl or fluroalkyl, preferably hydrogen, and a is from 1 to 12, preferably 1 to 6;

an oxaalkylene group such as alkoxyalkyl having 1 to 6 carbon atoms in each alkyl moiety, more preferably $-CH_2O(CH_2)_4-$; or

an oligo-oxaalkylene group of formula $-[(CR^5_2)_bO]_c(CR^5_2)_b-$ where the groups $-(CR^5_2)-$ are the same or different and in each group $-(CR^5_2)-$ the groups R^5 are the same or different and each group R^5 is hydrogen, fluorine or C_{1-5} alkyl or fluoroalkyl, preferably hydrogen, and b is from 1 to 6, preferably 2 or 3 and c is from 2 to 11, preferably 2 to 5; or

if X contains a carbon-carbon chain between B and the zwitterionic group or if Y contains a terminal carbon atom, a valence bond.

Preferred groups B include alkylene, oxaalkylene and oligo-oxaalkylene groups of up to 12 carbon atoms.

In compounds of formula (III) it is preferred that K and B contain up to 12 carbon atoms in total.

Preferred zwitterionic groups X are of formula (IVA), (IVB), (IVC), (IVD) and (IVE) as defined below: monomers containing such groups may be used in combination with further monomers containing polyurethane-like group to provide a copolymer of the invention. Of these groups of (IVB) are particularly preferred.

In addition, groups of formula (VA), (VB) and (VC) are preferred as monomers containing both a zwitterionic group and a group containing an -N(R)C(O)NR- or -N(R)C(O)O- moiety.

The groups of formula (IVA) are:

$$-\overset{+}{N}(R^6)_2-(CH_2)_d-SO_3^- \qquad \text{(IVA)}$$

where the groups R^6 are the same or different and each is hydrogen or C_{1-4} alkyl or the two groups R^6 form together with the nitrogen atom to which they are attached, a heterocyclic ring containing from 5 to 7 atoms and d is from 1 to 20.

Preferably the groups R^6 are hydrogen or C_{1-4} alkyl and preferably they are the same. It is also preferable that at least one of the groups R^6 is methyl, and more preferable that the groups R^6 are both methyl.

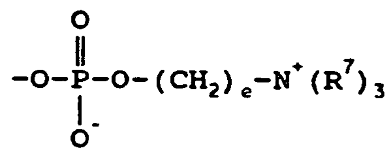
Preferably d is from 2 to 12, more preferably from 2 to 6, and even more preferably 2 to 4. Most preferably d is 3.

When X is a group of formula (IVA) preferably B is a group of formula $-(CR^4_2)-$ or $-(CR^4_2)_2-$, eg. $-(CH_2)-$ or $-(CH_2CH_2)-$.

Further zwitterionic groups include those corresponding to the groups of the formula (IVA) but which

contain a carboxylate or phosphate group in place of the sulphonate group.

The groups of formula (IVB) are:



(IVB)

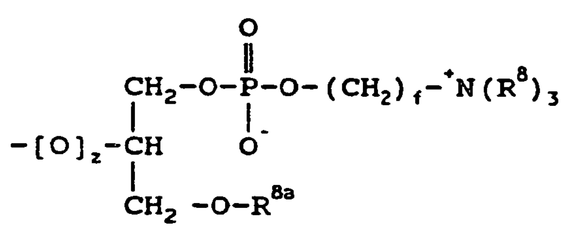
where the groups R^7 are the same or different and each is hydrogen, C_{1-4} alkyl, aryl, such as phenyl, or two of the groups R^7, together with the nitrogen atom to which they are attached, form a heterocyclic ring containing from 5 to 7 atoms or the three groups R^7, together with the nitrogen atom to which they are attached, form a fused ring structure containing from 5 to 7 atoms in each ring and e is from 1 to 20.

Preferably the groups R^7 are hydrogen or C_{1-4} alkyl and preferably they are the same. It is also preferable that at least one of the groups R^7 is methyl, and more preferable that the groups R^7 are all methyl.

Preferably e is preferably from 2 to 12, more preferably 2 to 6 and even more preferably 2 to 4. Most preferably e is 2.

When X is a group of formula (IVB) preferably B is a group of formula $-(CR^4{}_2)-$ or $-(CR^4{}_2)_2-$, eg. $-(CH_2)-$ or $-(CH_2CH_2)-$.

The groups of formula (IVC) are:



(IVC)

wherein the groups R^8 are the same or different and each is hydrogen, C_{1-4} alkyl aryl, such as phenyl, or two of the groups R^8, together with the nitrogen atom to which they are attached, form a heterocyclic ring containing from 5 to 7 atoms or the three groups R^8, together with the nitrogen

atom to which they are attached, form a fused ring structure containing from 5 to 7 atoms in each ring,

R^{8a} is hydrogen or, more preferably, a group $-C(O)B^1R^{8b}$ where R^{8b} is hydrogen or methyl, preferably methyl, B^1 is a valence bond or straight or branched alkylene, oxaalkylene or oligo-oxaalkalyene group,

f is from 1 to 20; and

if B is other than a valence bond z is 1 and if B is a valence bond z is 0, if X is directly bonded to an oxygen or nitrogen atom and otherwise z is 1.

Preferably the groups R^8 are hydrogen or C_{1-4} alkyl and preferably they are the same. It is also preferable that at least one of the groups R^8 is methyl, and more preferable that the groups R^8 are all methyl.

Preferably f is from 2 to 12, more preferably 2 to 6 and even more preferably from 2 to 4. Most preferably f is 2.

Preferably B^1 is:

a valence bond;

an alkylene group of formula $-(CR^{4a}{}_2)_{aa}-$, wherein the groups $-(CR^{4a}{}_2)-$ are the same or different, and in each group $-(CR^{4a}{}_2)-$ the groups R^{4a} are the same or different and each group R^{4a} is hydrogen or C_{1-4} alkyl, preferably hydrogen, and aa is from 1 to 12, preferably 1 to 6;

an oxaalkylene group such as alkoxyalkyl having 1 to 6 carbon atoms in each alkyl moiety, more preferably $-CH_2O(CH_2)_4-$; or

an oligo-oxaalkylene group of formula $-[(CR^{5a}{}_2)_{ba}O]_{ca}-$ where the groups $-(CR^{5a}{}_2)-$ are the same or different and in each group $-(CR^{5a}{}_2)-$ the groups R^{5a} are the same or different and each group R^{5a} is hydrogen or C_{1-4} alkyl, preferably hydrogen, and ba is from 1 to 6, preferably 2 or 3, and ca is from 1 to 12, preferably 1 to 6.

Preferred groups B^1 include a valence bond and alkylene, oxaalkylene and oligo-oxaalkylene groups of up to 12 carbon atoms.

Preferably B and B^1 are the same.

When X is a group of formula (IVC) preferably B is a group of formula $-[(CR^5{}_2CR^5{}_2)_bO]_cCR^5{}_2CR^5{}_2-$, eg. $-(CH_2CH_2O)_c(CH_2CH_2)-$.

The groups of formula (IVD) are:

$$-[O]_z-CH_2-\underset{\displaystyle O-R^{9a}}{\underset{|}{CH}}-CH_2-O-\underset{\displaystyle O^-}{\underset{|}{\overset{\displaystyle O}{\overset{\|}{P}}}}-O-(CH_2)_g-{}^+N(R^9)_3 \qquad \text{(IVD)}$$

wherein the groups R^9 are the same or different and each is hydrogen or C_1-C_4 alkyl, aryl, such as phenyl, or two of the groups R^9, together with the nitrogen atom to which they are attached, form a heterocyclic ring containing from 5 to 7 atoms or the three groups R^9, together with the nitrogen atom to which they are attached, form a fused ring structure containing from 5 to 7 atoms in each ring,

R^{9a} is a hydrogen or, more preferably, a group $-C(O)B^2R^{9b}$, R^{9b} is hydrogen or methyl, preferably methyl, B^2 is a valence bond or a straight or branched alkylene, oxaalkylene or oligo-oxaalkylene group,

g is from 1 to 20; and

if B is other than a valence bond z is 1 and if B is a valence bond z is 0 if X is directly bonded to an oxygen or nitrogen atom and otherwise z is 1.

Preferably the groups R^9 are hydrogen or C_{1-4} alkyl and preferably they are the same. It is also preferable that at least one of the groups R^9 is methyl, and more preferable that the groups R^9 are all methyl.

Preferably g is from 2 to 12, more preferably 2 to 6 and even more preferably 2 to 4. Most preferably g is 2.

Preferably B^2 is:

a valence bond;

an alkylene group of formula $-(CR^{4b}{}_2)_{ab}-$, wherein the groups $-(CR^{4b}{}_2)-$ are the same or different, and in each group $-(CR^{4b}{}_2)-$ the groups R^{4b} are the same of different and

each group R^{3b} is hydrogen or C_{1-4} alkyl, preferably hydrogen, and ab is from 1 to 12, preferably 1 to 6;

an oxaalkylene group such as alkoxyalkyl having 1 to 6, carbon atoms in each alkyl moiety, more preferably $-CH_2O(CH_2)_4-$; or

an oligo-oxaalkylene group of formula $-[(CR^{5b}_2)_{bb}O]_{cb}-$ where the groups $-(CR^{5b}_2)-$ are the same or different and in each group $-(CR^{5b}_2)-$ the groups R^{5b} are the same or different and each group R^{5b} is hydrogen or C_{1-4} alkyl, preferably hydrogen, and bb is from 1 to 6, preferably 2 or 3, and cb is from 1 to 12, preferably 1 to 6.

Preferred groups B^2 include a valence bond and alkylene, oxalkylene and oligo-oxalkylene groups of up to 12 carbon atoms.

Preferably B and B^2 are the same.

When X is a group of formula (IVD) preferably B is a group of formula $-[(CR^5_2CR^5_2)_bO]_cCR^5_2CR^5_2-$, eg. $-(CH_2CH_2O)_cCH_2CH_2-$.

The groups of formula (IVE) are:

$$\begin{array}{l} R^{10a}-O-CH_2 \quad\;\; O \\ \qquad\qquad\; | \qquad\quad \| \\ \qquad\qquad CH-O-P-O-(CH_2)_hN^+(R^{10})_3 \qquad \text{(IVE)} \\ \qquad\qquad\; | \qquad\quad | \\ -[O]_z-CH_2 \quad\;\; O^- \end{array}$$

wherein the groups R^{10} are the same or different and each is hydrogen, C_{1-4} alkyl, aryl, such as phenyl, or two of the groups R^{10}, together with the nitrogen atom to which they are attached, form a heterocyclic ring containing from 5 to 7 atoms or the three groups R^{10}, together with the nitrogen atom to which they are attached, form a fused ring structure containing from 5 to 7 atoms in each ring,

R^{10a} is hydrogen or, more preferably, a group $-C(O)B^3R^{10b}$ where R^{10b} is hydrogen or methyl, preferably methyl, B^3 is a valence bond or a straight or branched alkylene, oxaalkylene or oligo-oxaalkylene group,

h is from 1 to 20; and

if B is other than a valence bond z is 1 and if B is a valence bond z is 0 if X is directly bonded to the oxygen or nitrogen and otherwise z is 1.

Preferably the groups R^{10} are hydrogen or C_{1-4} alkyl and preferably they are the same. It is also preferable that at least one of the groups R^{10} is methyl, and more preferable that the groups R^{10} are all methyl.

Preferably h is from 2 to 12, more preferably 2 to 6, and even more preferably 2 to 4. Most preferably h is 2.

Preferably B^3 is:

a valence bond;

an alkylene group of formula $-(CR^{4c}{}_2)_{ac}-$, wherein the groups $-(CR^{4c}{}_2)-$ are the same or different, and in each group $-(CR^{4c}{}_2)-$ the groups R^{4c} are the same or different and each group R^{4c} is hydrogen or C_{1-4} alkyl, preferably hydrogen, and ac is from 1 to 12, preferably 1 to 6;

an oxaalkylene group such as alkoxyalkyl having 1 to 6 carbon atoms in each alkyl moiety, more preferably $-CH_2O(CH_2)_4-$; or

an oligo-oxaalkylene group of formula $-[(CR^{5c}{}_2)_{bc}O]_{cc}-$ where the groups $-(CR^{5c}{}_2)-$ are the same or different and in each group $-(CR^{5c}{}_2)-$ the groups R^{5c} are the same or different and each group R^{5c} is hydrogen or C_{1-4} alkyl, preferably hydrogen, and bc is from 1 to 6, preferably 2 or 3, and cc is from 1 to 12, preferably 1 to 6.

Preferred groups B^3 include a valence bond and alkylene, oxaalkylene and oligo-oxaalkylene groups of up to 12 carbon atoms.

Preferably B and B^3 are the same.

When X is a group of formula (IVF) preferably B is a group of formula $-[(CR^5{}_2CR^5{}_2)_bO]_cCR^5{}_2CR^5{}_2-$, eg. $-(CH_2CH_2O)_cCH_2CH_2-$.

Further zwitterionic groups include those corresponding to the formulae (IVB) to (IVE), but which contain in place of the ammonium group $-^{+}NR'_3$ a phosphonium

group $-^{+}PR'_r(OR')_{3-r}$ where r is from 0 to 3, or a sulphonium group $-^{+}SR'_2$, where R' corresponds to R^7, R^8, R^9 or R^{10} or a group Het^+, where Het is a nitrogen, phosphorous or sulphur-containing heterocycle, such as a pyridinium group.

Further zwitterionic groups include those which contain a sulphur atom, a group -NH- or a valence bond in place of either or both of the oxygen atoms bonding directly to the phosphorus of the phosphate group and to another atom in in the groups of formulae (IVB) to (IVE).

Further zwitterionic groups are of formula (VA), (VB) and (VC). These groups also contain a group capable of binding to a polymeric substrate surface by physisorption. Monomers containing such a group are therefore particularly suitable for use in the polymers of the invention, optionally without separate comonomers containing a group capable of binding to a polymeric surface by physisorption.

As a further feature the present invention provides compounds of formula (II) or (III) containing a zwitterionic group of formula (VA), (VB) or (VC).

The groups of formula (VA) are:

```
                  O
                  ‖
          CH2-O-P-O-(CH2)i-+N(R11)3        (VA)
          |       |
  -[O]z-CH        O-
          |
          CH2-O-R11a
```

wherein the groups R^{11} are the same or different and each is hydrogen, C_{1-4} alkyl, aryl, such as phenyl, or two of the groups R^{11}, together with the nitrogen atom to which they are attached, form a heterocyclic ring containing from 5 to 7 atoms or the three groups R^{11}, together with the nitrogen atom to which they are attached, form a fused ring structure containing from 5 to 7 atoms in each ring,

R^{11a} is a group of formula $-C(O)R^{11b}$, in which R^{11b} is a group containing an -NRC(O)NR- or -NRC(O)O- moiety capable

of stably binding to a polymeric substrate surface by physisorption,

i is from 1 to 20; and

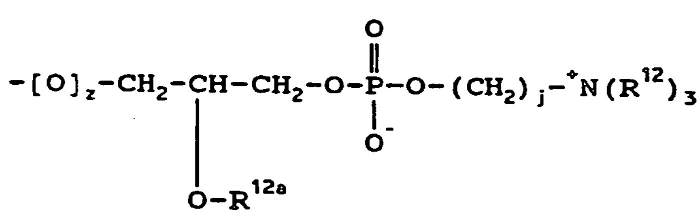
if B is other than a valence bond z is 1 and if B is a valence bond z is 0 if X is directly bonded to an oxygen or nitrogen atom and otherwise z is 1.

Preferably the groups R^{11} are hydrogen or C_{1-4} alkyl and preferably they are the same. It is also preferable that at least one of the groups R^{11} is methyl, and more preferable that the groups R^{11} are all methyl.

Preferably i is from 2 to 12, more preferably from 2 to 6, and even more preferably from 2 to 4. Most preferably i is 2.

Preferably the group R^{11b} is a group of formula (IXA) or (IXB) as defined hereinafter in relation to comonomers of formula (VII) and (VIII) which contain such a group.

The groups of formula (VB) are:



(VB)

wherein the groups R^{12} are the same or different and each is hydrogen, C_1-C_4 alkyl, aryl such as phenyl, or two of the groups R^{12}, together with the nitrogen atom to which they are attached, form a heterocyclic ring containing from 5 to 7 atoms or the three groups R^{12}, together with the nitrogen atom to which they are attached, form a fused ring structure containing from 5 to 7 atoms in each ring,

R^{12a} is a group of formula $-C(O)R^{12b}$, in which R^{12b} is a group containing an -NRC(O)NR- or -NRC(O)- moiety capable of stably binding to a polymeric substrate surface by physisorption;

j is from 1 to 20; and

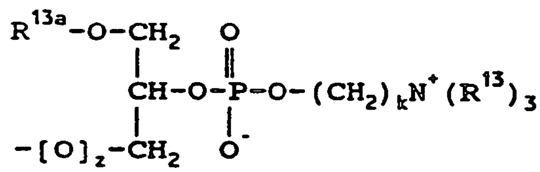
if B is other than a valence bond, z is 1 and if B is a valence bond z is 0 if X is directly bonded to an oxygen or nitrogen atom and otherwise z is 1.

Preferably the groups R^{12} are hydrogen or C_{1-4} alkyl and preferably they are the same. It is also preferable that at least one of the groups R^{12} is methyl, and more preferable that the groups R^{12} are all methyl.

Preferably j is from 2 to 12, more preferably from 2 to 6, and even more preferably from 2 to 4. Most preferably j is 2.

Preferably the group R^{12b} is a group of formula (IXA) or (IXB) as defined hereinafter in relation to comonomers of formula (VII) and (VIII) which contain such a group.

The groups of formula (VC) are:



(VC)

wherein the groups R^{13} are the same or different and each is hydrogen, $_{1-4}$ alkyl, aryl, such as phenyl, or two of the groups R^{13}, together with the nitrogen atom to which they are attached, form a heterocyclic ring containing from 5 to 7 atoms or the three groups R^{13}, together with the nitrogen atom to which they are attached, form a fused ring structure containing from 5 to 7 atoms in each ring,

R^{13a} is a group of formula $-C(O)R^{13b}$, in which R^{13a} is a group containing an -NRC(O)NR- or -NRC(O)- moiety capable of stably binding to a polyurethane substrate surface by physisorption;

k is from 1 to 20; and

if B is other than a valence bond, z is 1 and if B is a valence bond z is 0 if X is directly bonded to an oxygen or nitrogen atom and otherwise z is 1.

Preferably the groups R^{13} are hydrogen or C_{1-4} alkyl and preferably they are the same. It is also preferable that

at least one of the groups R^{13} is methyl, and more preferable that the groups R^{13} are all methyl.

Preferably k is from 2 to 12, more preferably from 2 to 6, and even more preferably from 2 to 4. Most preferably k is 2.

Preferably the group R^{13b} is a group (IXA) or (IXB) as defined hereinafter in relation to comonomer of formula (VII) and (VIII) which contain such a group.

Further zwitterionic groups include those corresponding to the formulae (VA) to (VC), but which contain in place of the ammonium group $-^{+}NR'_3$ a phosphonium group $-^{+}PR'_r(OR')_{3-r}$ where r is from 0 to 3, or a sulphonium group $-^{+}SR'_2$, where R' corresponds to R^{11}, R^{12}, or R^{13} or a group Het^{+}, where Het is a nitrogen, phosphorous or sulphur-containing heterocycle, such as a pyridinium group.

Further zwitterionic groups include those which contain a sulphur atom, a group -NH- or a valence bond in place of either or both of the oxygen atoms bonding directly to the phosphorus of the phosphate group and to another atom in formulae (VA) to (VC).

Particular examples of preferred monomers bearing a zwitterionic group are 2(methacryloyloxy)ethyl-2'(trimethylammonium)ethyl phosphate inner salt and 1[4(4'-vinylbenzyloxy)butane]- 2"(trimethylammonium)ethyl phosphate inner salt.

Monomers bearing a zwitterionic group such as those of formula (II) and (III) may be prepared by conventional techniques using known reactions, for example using a suitable substituted alkyl (alk)acrylate or suitable substituted styrene as precursor. Examples of suitable substituted alkyl (alk)acrylates include dimethylaminoethyl(meth)acrylate and 2-hydroxyethyl(meth)acrylate. The preparation of such monomers is described in WO 93/01221.

Alternatively monomers of formulae (IVB) to (IVE) may be obtained by reaction of NR'_3, ($R'=R^8$, R^9, R^{10} or R^{11}) with a corresponding compound containing a displaceable leaving

group such as halogen, alkylsulphonyloxy or arylsulphonyloxy in place of the ammonium group. Derivatives containing such displaceable groups may be obtained by the adaptation of known methods. Likewise comonomers containing other zwitterionic groups may be obtained by the adaptation of these or other methods.

Monomers of formula (II) or (III) containing a group of formula (VA), (VB) or (VC) may be prepared by direct analogy with methods for monomers containing groups of formula (IVC), (IVD) and (IVE) respectively. Similar methodology to that described in relation compounds of formula (VII) or (VIII) hereafter, may be used to introduce a group capable of binding to a polyurethane by physisorption, such as a group of formula (IXA) or (IXB).

<u>Comonomers containing a polyurethane-like group</u>

In the polymers of the invention, where the zwitterionic group and polyurethane-like pendant groups (containing an -N(R)C(O)N(R)- or -N(R)C(O)O- moiety) are not present in the residue of the same monomer, the polymer comprise residues of comonomer containing a polyurethane-like group as well as the residues of the comonomer containing a zwitterionic group. Optionally, where the monomer containing a zwitterionic group also contains a polyurethane-like group, further polyurethane-like groups may be provided by additional comonomer residues containing such groups.

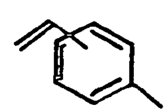
Preferred comonomers containing a polyurethane-like group are those of general formula (VI)

$$Y^1\text{-}Q \qquad \text{(VI)}$$

where Y^1 is an ethylenically unsaturated polymerisable group selected from

$$H_2C{=}\underset{}{\overset{\displaystyle R^{14}\atop |}{C}}{-}\underset{\displaystyle \| \atop O}{C}{-}A'{-}$$

or



K^1-

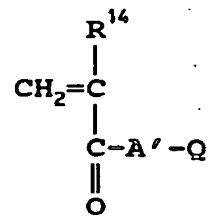
where R^{14} is hydrogen or C_1-C_4 alkyl,

A′ is -O- or $-NR^{15}-$ where R^{15} is hydrogen or a C_1-C_4 alkyl group or R^{15} is a group Q;

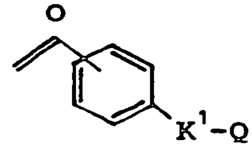
K^1 is a group $-(CH_2)_lOC(O)-$, $-(CH)_lC(O)O-$, $-(CH_2)_lOC(O)O-$, $-(CH_2)_lNR^{16}-$, $-(CH_2)_lNR^{16}C(O)-$, $-(CH_2)_lC(O)NR^{16}-$, $-(CH_2)_lNR^{16}C(O)O-$, $-(CH_2)_lOC(O)NR^{16}-$, $-(CH_2)_lNR^{16}C(O)NR^{16}-$ (in which the groups R^{16} are the same or different), $-(CH_2)_lO-$, $-(CH_2)_lSO_3-$, a valence bond and l is from 1 to 12 and R^{16} is hydrogen or a C_1-C_4 alkyl group; and

Q is a group containing an -NRC(O)NR- or -NRC(O)- moiety capable of stably binding to a polyurethane substrate surface by physisorption or capable of providing compatibility with a polyurethane polymer in a blend.

Preferred comonomers of formula (VI) bearing a group Q include those of formula (VII) and (VIII):



(VII)



(VIII)

wherein:

R^{14}, A′, K^1 and Q are as defined in relation to formula (VI).

Preferably in the compounds of formula (VII) R^{14} is hydrogen, methyl or ethyl, more preferably methyl so that the compound of formula (VII) is preferably an acrylic acid, methacrylic acid or ethacrylic acid derivative.

In the compounds of formula (VIII) K^1 may for instance be a valence bond. Where K^1 is a group then preferably l is from 1 to 6, more preferably 1, 2 or 3 and most preferably l is 1. When K^1 is a group $-(CH_2)_lNR^{16}-$, $-(CH_2)_lOC(O)NR^{16}-$, $-(CH_2)_lNR^{16}C(O)O-$, $-(CH_2)_lNR^{16}C(O)-$,

$-(CH_2)_tC(O)NR^{16}-$ or $-(CH_2)_tNR^{16}C(O)NR^{16}-$ then R^{16} is preferably hydrogen, methyl or ethyl, more preferably hydrogen.

In the compounds of formula (VIII), preferably the vinyl group is para to the group $-K^1-Q$.

Preferably Q is a group of formula (IXA) or (IXB)

$$-R^{17}-NRC(O)NR-R^{18} \qquad \text{(IXA)}$$

$$-R^{17}-NRC(O)O-R^{18} \qquad \text{(IXB)}$$

wherein R, (or the two groups R in (IXA), which may be the same or different each) is hydrogen or C_{1-4} alkyl;

R^{17} is alkylene, arylene, alkylarylene, arylalkylene or alkylarylalkylene, cycloalkylene, alkylcycloalkylene, cycloalkyl-alkylene or alkyl-cycloalkyl-alkylene; and

R^{18} is alkyl, aryl or alkylaryl or cycloalkyl or alkylcycloalkyl wherein the alkyl groups may optionally be interrupted by one or more arylene or cycloalkylene groups, and wherein R^{18} may optionally contain one or more groups -NRC(O)NR- or -NRC(O)O- as hereinbefore defined.

Compounds of formula (VII) and (VIII) which contain such a group (IXA) or (IXB) are provided as a further feature of the invention.

In (IXA) and (IXB), the groups R are preferably hydrogen, methyl or ethyl, more preferably hydrogen.

In R^{17}, alkylene groups may be straight or branched, preferably straight, and preferably contain from 1 to 6 carbon atoms, for example $-(CH_2)_{1-6}-$. Arylene groups are preferably meta- or para-, more preferably para-, disubstituted and are preferably phenylene groups. Arylene groups may optionally be further substituted for example by one or more alkyl or alkoxy groups of 1 to 4 carbon atoms. Cycloalkylene groups may for example contain from 5 to 7 carbon atoms in the cycloalkyl ring. Preferably such groups are disubstituted cyclohexyl for example 1,4-cyclohexyl. Cycloalkylene groups may optionally be further substituted for example by one or more alkyl or alkoxy groups of 1 to 4 carbon atoms.

Particularly preferred groups R^{17} are $-(CH_2)_{1-6}-$, arylene-containing groups chosen from $-(C_6H_4)-$, $-CH_2(C_6H_4)-$,

$-(C_6H_4)CH_2-$ and $-CH_2(C_6H_4)CH_2-$ and cycloalkylene-containing groups chosen from $-(C_6H_{10})-$, $-CH_2(C_6H_{10})-$, $-(C_6H_{10})CH_2-$ and $-CH_2(C_6H_{10})CH_2-$. $-CH_2CH_2-$ is most preferred.

In R^{18}, alkyl groups may be straight or branched, preferably straight, and preferably contain from 1 to 10 for instance 1 to 6 carbon atoms. Aryl groups may for example by phenyl groups and arylene groups are preferably meta- or para-, more preferably para-, disubstituted and are preferably phenylene groups. Aryl and arylene groups may optionally be substituted for example by one or more alkyl or alkoxy groups of 1 to 4 carbon atoms. Cycloalkyl and cycloalkylene groups may for example contain from 5 to 7, more preferably 6, carbon atoms in the cycloalkyl ring. Preferably cycloalkylene groups are disubstituted cyclohexyl for example 1,4-cyclohexyl. Cycloalkyl and cycloalkylene groups may optionally be substituted for example by one or more alkyl or alkoxy groups of 1 to 4 carbon atoms.

Particularly preferred groups R^{18} are:

$$-(R^{18a}-NRC(O)NR)_n-R^{18b}$$

or $$-(R^{18a}-NRC(O)O)_n-R^{18b}$$

where n is from 0 to 6, preferably 0 to 3, more preferably 0 or 1 and the groups R^{18a} are the same or different and each is $-(CH_2)_{1-10}-$ preferably $-(CH_2)_{1-6}-$, an arylene-containing group which is $-C_6H_4-$, $-(CH_2)_{1-6}(C_6H_4)-$ preferably $-CH_2C_6H_4-$, $-(C_6H_4)(CH_2)_{1-6}(C_6H_4)-$ preferably $-(C_6H_4)(CH_2)(C_6H_4)-$, or $-(CH_2)_{1-6}(C_6H_4)(CH_2)_{1-6}(C_6H_4)-$ preferably $-CH_2(C_6H_4)CH_2(C_6H_4)-$, or a cycloalkylene-containing group which is $-C_6H_{10}-$, $-(CH_2)_{1-6}(C_6H_{10})-$ preferably $-CH_2C_6H_{10}-$, $-(C_6H_{10})(CH_2)_{1-6}(C_6H_{10})-$ preferably $-(C_6H_{10})(CH_2)(C_6H_{10})-$, or $-(CH_2)_{1-6}(C_6H_{10})(CH_2)_{1-6}(C_6H_{10})-$ preferably $-CH_2(C_6H_{10})CH_2(C_6H_{10})-$,

and R^{18b} is $-(CH_2)_{1-9}CH_3$ preferably $-(CH_2)_{1-5}CH_3$, an aryl-containing group which is $-C_6H_5$, $-(CH_2)_{1-6}(C_6H_5)$ preferably $-CH_2C_6H_5$, $-(C_6H_4)(CH_2)_{1-6}(C_6H_5)$ preferably $-(C_6H_4)(CH_2)(C_6H_5)$ or $-(CH_2)_{1-6}(C_6H_4)(CH_2)_{1-6}(C_6H_5)$, preferably $-CH_2(C_6H_4)CH_2(C_6H_5)$, or a cycloalkyl-containing group which $-C_6H_{11}$, $-(CH_2)_{1-6}(C_6H_{11})$ preferably $-CH_2C_6H_{11}$, $-(C_6H_{10})(CH_2)_{1-6}(C_6H_{11})$ preferably $-(C_6H_{10})(CH_2)(C_6H_{11})$ or $-(CH_2)_{1-6}(C_6H_{10})(CH_2)_{1-6}(C_6H_{11})$ preferably

$-CH_2(C_6H_{10})CH_2(C_6H_{11})$.

In the case where R^{17} and R^{18} together contain more or less than one aryl or cycloalkyl moiety, these moieties may contain the same or a different aryl or cycloalkyl ring. Preferably the aryl or cycloalkyl rings are the same.

Particular examples of compounds containing a group (IXA) or (IXB) are:

phenylaminocarbonylaminophenylmethylphenylamino-carbonylaminoethyl methacrylate;
cyclohexylaminocarbonylaminocyclohexylmethyl-cyclohexylaminocarbonylaminoethyl methacrylate;
butyloxycarbonylaminoethyl methacrylate;
benzyloxycarbonylaminoethyl methacrylate;
phenyloxycarbonylaminoethyl methacrylate; and
cyclohexyloxycarbonylaminoethyl methacylate.

According to a further feature the present invention provides a process for producing a compound of formula (VII) or (VIII) which contains a group (IXA) or (IXB) which process comprises reacting a corresponding compound containing, in place of the group of formula (IXA) or (IXB), a group of formula (X)

$$-R^{17}-NCO \quad (X)$$

where R^{17} is as hereinbefore defined with

(a) a compound $R^{18}-NH_2$ or an activated derivative thereof where R^{18} is as hereinbefore defined to produce a compound containing a group of formula (IXA); or

(b) a compound $R^{18}-OH$, or an activated derivative thereof where R^{18} is as hereinbefore defined to produce a compound containing a group of formula (IXB).

The reactions are generally carried out in the presence of a solvent. They may be carried out at a temperature from 0 to 150°C, for example from 20 to 70°C in non-protic solvents such as DMSO, DMF, dimethylacetamide, toluene, benzene, hexane or cyclohexane. Reaction may be

carried out in the presence of a catalyst such as dibutyl tin dilaurate.

Compounds $R^{18}-NH_2$ and $R^{18}-OH$ may be produced by using known methods. Compounds containing an isocyanate group of formula (X) may likewise be produced by known methods, for example as described in Advanced Organic Chemistry, J. March, published by J. Wiley & Sons, 1985.

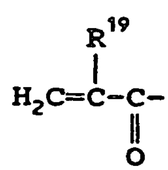
<u>Comonomers bearing a reactive group</u>

Residues of comonomers bearing a reactive group may optionally be present in copolymers of the invention to introduce functionality for the attachment of ligand groups or to introduce crosslinkable groups. However the proportion of such comonomer residues must be sufficiently small so that the copolymer's ability to bind to a polymeric by physisorption or compatibility for blending with a base polymer is not substantially impaired and so that the copolymer is not rendered water soluble.

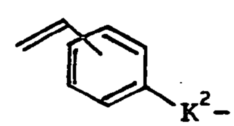
Preferred comonomers, containing a reactive group capable of providing covalently bonding to a moiety are of general formula (XI)

$$Y^2-Q^1 \qquad (XI)$$

where Y^2 is an ethylenically unsaturated polymerisable group selected from



or



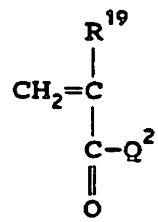
where R^{19} is hydrogen or C_1-C_4 alkyl,

K^2 is a group $-(CH_2)_qOC(O)-$, $-(CH)_qC(O)O-$, $-(CH_2)_qOC(O)O-$, $-(CH_2)_qNR^{20}-$, $-(CH_2)_qNR^{20}C(O)-$, $-(CH_2)_qC(O)NR^{20}-$, $-(CH_2)_qNR^{20}C(O)O-$, $-(CH_2)_qOC(O)NR^{20}-$, $-(CH_2)_qNR^{20}C(O)NR^{20}-$ (in which the groups R^{20} are the same or different), $-(CH_2)_qO-$, or $-(CH_2)_qSO_3-$, or a valence bond and q is from 1 to 12 and R^{20} is hydrogen or a C_1-C_4 alkyl group; and

Q^1 is a reactive group capable of reacting to provide covalent bonding.

Preferred comonomers of formula (XI) bearing a reactive group Q^1 include those of formula (XII) and (XIII) defined below.

The compounds of formula (XII) are:



(XII)

wherein:

R^{19} is as defined with reference to formula (XI), and Q^2 is a reactive group.

Preferably in the compounds of formula (XII) R^{19} is hydrogen, methyl or ethyl, more preferably methyl, so that the compound of formula (XII) is preferably an acrylic acid, methacrylic acid or ethacrylic acid derivative.

Preferably Q^2 is hydrogen, or more preferably -OH or a group of the formula:

$$-T-B^7-Q^3$$

where T is -O-, or $-NR^{21}-$ where R^{21} is hydrogen, C_1-C_4 alkyl or a group $-B^7-Q^3$;

B^7 is a valence bond or, more preferably, a straight or branched alkylene, oxaalkylene or oligo-oxaalkylene chain; and

Q^3 is a reactive group capable of reacting to provide covalent bonding.

Preferably B^7 is:

an alkylene group of formula $-(CR^{22}_2)_r-$, wherein the groups $-(CR^{22}_2)-$ are the same or different, and in each group $-(CR^{22}_2)-$ the groups R^{22} are the same or different and each group R^{22} is hydrogen or C_{1-4} alkyl, preferably hydrogen, and r is from 1 to 12, preferably 1 to 6;

an oxaalkylene group such as alkoxyalkyl having 1 to 6 carbon atoms in each alkyl moiety; or

an oligo-oxaalkylene group of formula $-[(CR^{23}_2)_sO]_t(CR^{23}_2)_s-$ where the groups $-(CR^{23}_2)-$ are the same or different and in each group $-(CR^{23}_2)-$ the groups R^{23} are

the same or different and each group R^{23} is hydrogen or C_{1-4} alkyl, preferably hydrogen, and s is from 1 to 6, preferably 2 or 3, and t is from 1 to 11, preferably 1 to 5.

Preferred reactive comonomers which are used to crosslink the comonomer, are those of formula (XII) or (XIII) in which Q^2, or Q^4 contains a crosslinkable group such as a cinnamyl, epoxy, $-CHOHCH_2Hal$ (in which Hal is a halogen atom), methylol or silyl group, an ethylenically unsaturated crosslinkable group such as an acetylenic, diacetylenic, vinylic or divinylic group, an acetoacetoxy group or chloroalkyl sulfone, preferably chloroethyl sulphone, group.

Particular examples of comonomers bearing a group capable of crosslinking include methacrolein, cinnamyl methacrylate, 2,3-epoxypropyl methacrylate, 3-chloro-2-hydroxypropyl methacrylate, hydroxymethyl methacrylamide, 3-(trimethoxysilyl)propyl methacrylate, 2-acetoacetoxyethyl methacrylate, 3-(vinylbenzyl)-2-chloroethyl sulfone.

When a polymer of the invention, containing crosslinkable groups, is coated on a substrate the polymer is in substantially uncrosslinked form. After coating, crosslinking of crosslinkable groups may be performed to increase the strength and stability of the polymer coating.

Comonomers containing a reactive group, such as compounds of formula (XII) and (XIII) may alternatively be used as comonomers which provide means for the attachment of a ligand to the copolymers of the invention.

Preferred reactive comonomers which are used to provide such means of attachment are those of formula (XII) or (XIII) where Q^2 or Q^4 is a hydroxyl, amino or carboxylic acid group or an activated derivative thereof such as a succinimido, tosylate, triflate, imidazole carbonyl-amino or substituted triazine group. Preferably such a reactive group Q^2 or Q^4 is separated from the copolymer chain by a spacer group, B^7 or B^8 of sufficient to allow the functional group Q^2 or Q^4 to interact with ligand. Alternatively such compounds may be used for the attachment of other molecules

to the copolymer, such as molecules which will then interact with a ligand.

It will be appreciated that the number of sites for the attachment of such a ligand or other molecules to a surface may be varied by varying the proportion of comonomer containing reactive groups in the copolymer used to coat the surface.

Comonomers containing a reactive group, such as those of formula (XII) and (XIII) may be obtained by known methods or by the adaptation thereof.

Diluent Comonomers

The polymers of the present invention may optionally comprise residues of a diluent comonomer, in addition to zwitterionic comonomer and comonomer containing a polyurethane-like to group.

Such diluent comonomers may be used to give the polymer the desired physical and mechanical properties. They may be of any known conventional radical polymerisable, preferably ethylenically unsaturated, type compatible with other comonomer(s).

Particular examples of diluent comonomers include alkyl(alk)acrylate preferably containing 1 to 30, more preferably 1 to 12, for example 1 to 4 carbon atoms in the alkyl group of the ester moiety, such as methyl (alk)acrylate; a dialkylamino alkyl(alk)acrylate, preferably containing 1 to 4 carbon atoms in each alkyl moiety of the amine and 1 to 4 carbon atoms in the alkylene chain, e.g. 2-(dimethylamino)ethyl (alk)acrylate; an alkyl (alk)acrylamide preferably containing 1 to 4 carbon atoms in the alkyl group of the amide moiety; a hydroxyalkyl (alk)acrylate preferably containing from 1 to 4 carbon atoms in the hydroxyalkyl moiety, e.g. a 2-hydroxyethyl (alk)acrylate; or a vinyl monomer such as an N-vinyl lactam, preferably containing from 5 to 7 atoms in the lactam ring, for instance vinyl pyrrolidone; styrene or a styrene derivative which for example is substituted on the phenyl ring by one or more alkyl groups containing from 1 to 6, preferably 1 to 4, carbon atoms, and/or by one or

more halogen, such as fluorine atoms, e.g. (pentafluorophenyl)styrene.

Other suitable diluent comonomers include polyhydroxyl, for example sugar, (alk)acrylates and (alk)acrylamides in which the alkyl group contains from 1 to 4 carbon atoms, e.g. sugar acrylates, methacrylates, ethacrylates, acrylamides, methacrylamides and ethacrylamides. Suitable sugars include glucose and sorbitol. Particularly suitable diluent comonomers include methacryloyl glucose or sorbitol methacrylate.

Further diluents which may be mentioned specifically include polymerisable alkenes, preferably of 2-4 carbon atoms, eg. ethylene, dienes such as butadiene, alkylene anhydrides such as maleic anhydride and cyano-substituted alkylenes, such as acrylonitrile.

Diluent comonomers may be obtained by conventional known methods.

Of the above diluent comonomers some are inert and act simply to modify the physical and mechanical properties of copolymers containing them. Others, and in particular the hydroxyalkyl(alk)acrylates and polyhydroxyl (alk)acrylates have a reactive role in addition to simply modifying physical and mechanical properties. Such comonomers contain functional groups, such as hydroxyl groups, which may react with a crosslinking group or may react with reactive groups in other molecules to attach them to the copolymer.

According to a feature of the present invention polymers of the invention may be prepared by:

a) copolymerising a comonomer containing a zwitterionic group, a comonomer containing a polyurethane-like group, a diluent and/or reactive comonomer; or

b) polymerising a monomer containing a zwitterionic group, and a polyurethane-group, a diluent and/or a reactive comonomer.

Any conventional technique may be used for polymerisation, typically thermal or photochemical polymerisation. Where comonomers capable of producing

crosslinking in the coated polymer film are present, the polymerisation condition are set such that crosslinking does not occur during polymerisation. Thus, for example, actinic radiation would not be used to prepare a polymer containing a comonomer which can form crosslinks by exposure to actinic radiation.

For thermal polymerisation a temperature from 40 to 100°C, typically 50 to 80°C is used. For photochemical polymerisation actinic radiation such as gamma, U.V., visible, or microwave radiation may be used. Typically U.V. radiation of wavelength 200 to 400 nm is used.

The polymerisation is generally performed in a reaction medium, which is for instance a solution or dispersion using as a solvent for example acetonitrile, dimethyl formamide, chloroform, dichloromethane, ethyl acetate, dimethyl sulphoxide, dioxan, benzene, toluene, tetrahydrofuran, or where the polymer does not contain groups which react with protic solvents, water or an alkanol containing from 1 to 4 carbon atoms, e.g. methanol, ethanol or propan-2-ol. Alternatively, a mixture of any of the above solvents may be used.

The polymerisation may be carried out in the presence of one or more polymerisation initiators, such as benzoyl peroxide, 2,2'-azo-bis(2-methylpropionitrile) or benzoin methyl ether. Other polymerisation initiators which may be used are disclosed in "Polymer Handbook", 3rd edition, Ed. J. Brandrup and E.H. Immergut, Pub. Wiley-Interscience, New York, 1989.

Generally the copolymerisation is performed for 1 to 72 hours, preferably 4 to 48, for instance 16 to 24 hours, and under an inert atmosphere of for example nitrogen or argon. The polymer is generally purified by dialysis, precipitation in a non-solvent (e.g. diethyl ether or acetone) or ultrafiltration. The resulting polymer is generally dried under vacuum, eg. for 5 to 72 hours and has a molecular weight from 10,000 to 10 million, preferably from 20,000 to 1 million.

The precise proportion and nature of the various comonomers used to prepare a copolymer according to the present invention comprising residues of a zwitterionic comonomer and a comonomer containing a polyurethane-like group may be adjusted to provide a copolymer which is particularly suitable for coating a particular surface or compatibility with a particular base polymer in a blend. Thus the proportion and nature of comonomer containing a polyurethane-like group may be adapted to provide efficient physisorption at a particular polymeric surface or compatibility with a particular base polymer in a blend. Similarly the proportion of the comonomer containing a zwitterionic group and of diluent and/or reactive comonomer may be adapted to provide the desired biocompatibility and physical and mechanical properties. It will be appreciated that to obtain the desired combination of properties more than one type of comonomer containing a zwitterionic group, comonomer containing a group capable of stably binding the polymer to a surface or crosslinkable and/or diluent comonomer may be used.

Similarly, in polymers comprising residues of a monomer containing a zwitterionic group and a polyurethane-like group, the nature of these groups may be adjusted to provide the desired biocompatibility and efficient binding at a particular surface, as well as desired physical and mechanical properties. Where, in addition, a diluent and/or crosslinkable comonomer is used the nature of the diluent and/or crosslinkable comonomer and the proportions of the comonomers may be likewise adjusted. It will again be appreciated that to obtain the desired combination of properties more than one type of monomer containing a zwitterionic group and a polyurethane-like group and/or more than one type of crosslinkable and/or diluent comonomer may be used.

Where different comonomers are used to provide the zwitterionic group and the physisorption, then preferably the molar ratio in the copolymer of zwitterionic comonomer residues to comonomer residues containing a polyurethane-

like group is from 5:95 to 90:10, more preferably 10:90 to 75:25. Preferably the molar ratio of zwitterionic comonomer residues to comonomer residues containing a polyurethane-like group and diluent comonomer residues is from 5:95 to 80:20, more preferably 10:90 to 50:50.

The copolymer preferably comprises from 5% to 75%, more preferably 10% to 60%, by mole residues of diluent monomer and/or from 0.1% to 20%, more preferably 1% to 10%, by mole residues of reactive comonomer, provided that where residues of both diluent and reactive comonomer are present, they do not exceed in combination 75%, preferably 60% by mole.

In addition the monomer or comonomer composition may comprise further components such as a polymerisation initiator, chain transfer agent, acid, base, surfactant, emulsifier or catalyst of conventional type each in an amount from 0.1% to 5%, typically from 0.2% to 3% and preferably about 0.5%, by weight each relative to the total weight of the monomers.

As a further feature the present invention provides a process for biocompatibilising a polymeric substrate surface which comprises coating the surface with a polymer according to the present invention. Various types of surfaces may be coated depending upon the nature of the groups in the polymer capable of binding it to the surface.

Treatment with such a polymer is generally carried out by coating the surface with a solution, dispersion (including a microdispersion) of the polymer, generally in an alcoholic, aqueous, organic or halogenated solvent or a mixture thereof, e.g. methanol, ethanol, dichloromethane or freon. The treatment is generally carried out at ambient or elevated temperature, such as from 5 to 60°C.

Polymeric substrates may be coated with polymers of the invention by known techniques, such as dip-coating, spray-coating, web-coating or spin coating.

The polymers of the present invention are particularly suitable for treating the following polyurethane substrates:

Esthane, Ostamer, Biomer, Pellethane, Lycra, Spandex, Mitrathane, Cardiothane and Tecoflex.

After coating the polymer may be crosslinked if it contains the residues of crosslinkable comonomer by known method for crosslinking the specific crosslinkable groups which are present. Crosslinking may, for instance, be introduced thermally, using actinic radiation, using reactive gases for example ammonia by changing the pH, using difunctional additives or by using activation chemistries for example by known methods as described in "Methods in Enzymology, volume 135, Immobilised Enzymes and Cells, part B", Ed. K. Mosbach, Academic Press Inc, New York, 1987. This activation may be performed on the dry coating, in the cases of thermal radiation or gas treatment. Alternatively for cases where the pH needs to be changed or additives need to be included, activation may be performed on the coated material in a solution which does not remove the coating.

Polymeric materials having surfaces coated according to the present invention can be used as components for implants or prostheses for the human or animal body, particularly where these implants or prostheses are to come into direct physical contact with blood and where biocompatibility and particularly haemocompatibility are required e.g. in heart valves. They can also be used in the construction of membranes and other devices that are to be brought into contact with blood or other body fluids on an extra-corporeal basis, for example in heart-lung machines or artificial kidneys.

Additionally the polymers of the invention can be used to coat materials employed in down stream processing applications e.g. separation membranes and process equipment and tubing. In particular the materials of the invention can be used to modify the surface properties of biofiltration membranes in bioreactors and fermentation systems, where the membranes come into direct contact with complex biological solutions containing e.g. proteins, polysaccharides, fats and even whole cells. They may also

be used in membranes which come into contact with microorganisms, such as bacteria, to prevent adhesion of such microorganisms. The polymers of the invention are particularly useful in reducing membrane fouling by the components of a process solution.

When the polymers of the present invention are used to coat the surface of a material which is then used in the construction coat of finished devices, it may be necessary to take precautionary steps to ensure that the coated surface is not damaged and the effectiveness of the treatment reduced before the finished device is produced.

In addition, the polymers of the present invention can be used to coat finished implants, prostheses, membranes, catheters, and other devices which are coated with a polymer according to the present invention to impart biocompatibility to the article.

The invention thus also provides a finished device comprising a polymeric substrate surface having a coating thereon of a polymer of the present invention.

According to a further feature of the present invention, the polymers of the invention may be blended with a base polymer having desirable physical and/or mechanical properties to provide a blend combining the physical and/or mechanical properties of the base polymer with improved biocompatibility.

The present invention therefore further provides a blend comprising (A) a polymer according to the present invention and (B) a base polymer and a process for producing such a blend which comprises blending the polymers (A) and (B).

In particular such blends may comprise, as base polymer a polyurethane (B), such as Esthane, Ostamer, Biomer, Pellethane, Lycra, Spandex, Mitrathane, Cardiothane or Tecoflex.

Generally such blends will contain from 1 to 90% by weight of polymer (A) containing pendant zwitterionic groups and from 99 to 10% of base polymer (B) having desirable physical and/or mechanical properties. The

precise proportions of the polymers (A) and (B) will depend upon the compatibility of the two polymers for blending and, it may be necessary to test the polymers together for their compatibility. This may be achieved by blending different proportions of the polymers (A) and (B) to obtain a blend with the desired balance of mechanical and physical properties as well as biocompatibility. In particular, the proportions of the two polymers may be adjusted so as to obtain desired impact resistance, tensile strength, flexural modulus, low temperature brittleness, friction co-efficient film permeability, film tear resistance, film shrinkage, surface and volume resistivity, surface wettability and/or contact angle.

The minimum quantity of polymer of the invention (A) will depend upon the particular polymer (B), the content of zwitterionic groups in the polymer (A) and the desired use of the blend. However, the content of polymer (A) should be sufficient to provide a detectable modification to the biocompatible properties of the blend compared to the unblended polymer (B). Preferably the blend will contain at least 1%, more preferably 10% and still more preferably 30% of polymer (A).

In addition, the blends of the present invention may further comprise conventional additives used in polymeric materials such as plasticisers, fillers, colourants, UV absorbers, anti-oxidants and/or preservatives, such as biocides, which may be included in conventional amounts so as to be compatible with the polymers present in the blend.

The blending of the two polymers (A) and (B) may be carried out by conventional techniques for blending polymeric materials, including known solid state physical mixing techniques such as roll-milling, Banbury mixing, screw extrusion and disk compounding. Alternatively, blending may be carried out using dispersions and/or solutions of the polymers (A) and (B) in an organic solvent and the solvent removed by evaporation. Such blending may be carried out using conventional liquid phase blending techniques such as high or low shear mixers.

The invention further provides a shaped article formed from a blend of polymer of the invention and a base polymer. Such articles may be formed in a conventional manner, for example by extrusion or injection moulding or other moulding techniques and/or by machining as necessary for the desired end shape appropriate to the nature of the particular material in question.

In particular, such blends may be suitable for use in surgical implants, bioseparation apparatus, blood carrier bags, dialysis membranes, blood oxygenator films, tubing, connectors, stoppers, closures for diagnostic catheters, surgical drapes and tapes, and encapsulants for bio-medical applications. They may in particular be used in the production of prostheses, artificial hearts and vascular surfaces.

The following figures illustrate the present invention:

Figure 1 shows the structure of two polyurethanes, Pellethane and TM3 which have been used as substrates onto which copolymers of the present invention have been coated as described in example 7.

Figures 2 and 3 show scanning electronmicrographs of the products of Example 8.

The present invention will now be further illustrated by the following Examples:-

EXAMPLE 1

Butyloxycarbonylaminoethyl-methacrylate

Isocyanate ethyl methacrylate (0.1 mol, 15.5 g), n-butanol (0.105 mol, 7.78 g), toluene (150 mL) and a small amount of dibutyltin dilaurate were stirred at 60°C for 4.5 hours. After the reaction, toluene was removed with an evaporator and butyloxycarbonylaminoethyl-methacrylate was obtained by distillation under reduced pressure.

^{1}H-NMR:(CDCl$_3$, σ in ppm) 0.83-0.88 (α-CH$_3$, 3H), 1.26-1.55(CH$_2$ and CH$_3$ in side chain, 7H), 3.40-3.43(CH$_2$-N, 2H), 3.95-4.05(NCOO-CH$_2$, 2H), 4.10-4.17(CCOO-CH$_2$, 2H), 4.80-4.95(-NHCOO-, 1H), 5.52-5.53(C=CH, 1H), 6.05-6.06(C=CH, 1H); IR:(cm^{-1}) 3200-3400(-NHCOO-), 2800-3000(CH$_2$ and CH$_3$),

1720(C=0), 1640(C=CH2), 1580(-NHCOO-), 1100-1260(-COO-). Elemental analysis: found(calc.). C: 57.33 (57.62), H: 8.37 (8.35), N5.83 (6.11). B. pt 132-135°C at 2 mm Hg.

EXAMPLE 2

Benzyloxycarbonylaminoethyl-methacrylate

Benzyloxycarbonylaminoethyl-methacrylate was prepared by a method analogous to that of Example 1 but using benzyl alcohol (0.105 mol, 11.3 g) in place of n-butanol and a reaction time of 3 hours. The reaction mixture was cooled to 0°C and the product obtained by crystallisation.

^{1}H-NMR:($CDCl_3$, σ in ppm) 1.85-1.90 (α-CH_3, 3H), 3.44-3.45(CH_2-N, 2H), 3.95-4.05(NCOO-CH_2, 2H), 4.15-4.17(CCOO-CH_2, 2H), 4.95-4.98(-NHCOO-, 1H), 5.00-5.04(NCOCH_2-, 2H), 5.50-5.51(C=CH, 1H), 6.00-6.03(C=CH, 1H); 7.17-7.29(C_6H_5-, 5H); IR:(cm^{-1}) 3250-3350(-NHCOO-), 2800-3000(CH_2 and CH_3), 1720(C=0), 1640(C=CH2), 1600(aromatic ring), 1580(-NHCOO-), 1100-1260(-COO-). Elemental analysis: found(calc.). C: 63.99 (64.14), H: 6.50 (6.51), N: 5.30 (5.32), M. pt 36.3°C.

EXAMPLE 3

Phenyloxycarbonylaminoethyl-methacrylate

Phenyloxycarbonylaminoethyl-methacrylate was prepared by a method analogous to that of Example 2 but using phenol (0.105 mol, 9.88 g) in place of benzyl alcohol and a reaction time of 19.5 hours. The reaction mixture was cooled to 0°C and the product obtained by crystallisation.

^{1}H-NMR:($CDCl_3$, σ in ppm) 1.97(α-CH_3, 3H), 3.57-3.60(CH_2-N, 2H), 4.29-4.31(CCOO-CH_2, 2H), 5.35(-NHCOO-, 1H), 5.61-5.62(C=CH, 1H), 6.16(C=CH, 1H), 7.11-7.37(C_6H_5-, 5H); IR:(cm^{-1}) 3280-3380(-NHCOO-), 2800-3000(-CH_2- and -CH_3), 1720(C=0), 1640(C=CH2) 1580(-NHCOO-), 1500(aromatic ring), 1100-1260(-COO-). Elemental analysis: found (calc.). C: 62.60 (62.64), H: 5.09 (6.06), N: 5.49 (5.62), M. pt 111.0°C.

EXAMPLE 4

Poly(2(methacryloyloxy)ethyl)-2-(trimethyl ammonium) ethyl phosphate inner salt - co-butyl methacrylate-co-butyloxycarbonylaminoethyl-methacrylate (36:53:11)

2(Methacryloyloxy ethyl)-2'(trimethylammonium) ethyl phosphate inner salt, butylmethacrylate, butyloxycarbonylaminoethyl-methacrylate in a molar ratio 30:60:10 were dissolved in ethanol (30 ml) at a concentration of 1 M in a glass ampoule. 2,2'-azobisisobutyronitrile (AIBN) was dissolved in the solution at 1 mM. Argon was bubbled through the solution to remove oxygen and the glass ampoule was sealed. Reaction was carried out at 60°C for 4 hours. The reaction mixture was allowed to cool and poured into a mixture of diethyl ether: N,N-dimethyl formamide (9:1 vol) to remove unreacted monomer and precipitate polymer. The precipitate was filtered and dried under reduced pressure. Yield 40.8% of polymer, Molecular weight 38,000, determined by GPC with poly(oxyethylene) standard.

The ratio of the comonomer residues in the copolymer was determined by elemental analysis from phosphorous content (in the phosphorous inner salt residues) and nitrogen content (in phosphorous inner salt and urethane residues).

IR: (cm^{-1}) 3000-3500(-NHCOO-), 2800-2900(CH_2, CH_3), 1740(C=O), 1200-1300(-COO-), 1000-1200($-OPO(=O)(O^-)-$)

EXAMPLE 5

Poly(2(methacryloyloxy)ethyl)-2-(trimethyl ammonium) ethyl phosphate inner salt -co-butyl methacrylate-co-benzyloxycarbonylaminoethyl-methacrylate (26:63:9)

By a procedure analogous to that of Example 4 but using benzyloxycarbonylaminoethyl-methacrylate, in place of butyloxycarbonylaminoethyl-methacrylate polymer was obtained in 55.6% yield. The polymer showed a molecular weight of 59,000 as determined by GPC with poly(oxyethylene) standard and the content of the comonomer residues was determined as in Example 4. Absorption peaks

similar to those in the IR spectrum given in Example 4 were observed.

EXAMPLE 6

Poly(2(methacryloyloxy)ethyl)-2-(trimethyl ammonium) ethyl phosphate inner salt -co-butyl methacrylate-co-phenyloxycarbonylaminoethyl-methacrylate (30:58:12)

By a procedure analogous to that of Example 4 but using phenyloxycarbonylaminoethyl-methacrylate in place of butyloxycarbonylaminoethyl-methacrylate polymer was obtained in 43.9% yield. The polymer showed a molecular weight of 41,000 as determined by GPC with poly(oxyethylene) standard and the content of the comonomer residues was determined as in Example 4. Absorption peaks similar to those in the IR spectrum given in Example 4 were observed.

EXAMPLE 7

Coating of polyurethane membrane

Polyurethane membranes were prepared by solvent evaporation. The polyurethane was dissolved in tetrahydrofuran and the solution poured onto a teflon plate. The solvent was allowed to evaporate at room temperature and the membrane formed was dried under reduced pressure at 40°C removing residual solvent. The membrane thus produced had a thickness of 0.3 mm. Membranes were prepared using the polyurethanes Pellethane and TM-3 whose structures are shown in Figure 1.

Polyurethane Pellethane and TM-3 membranes were coated with the copolymers of Examples 4 to 6 and, as a comparison, a copolymer of 2(methacryloyloxyethyl)-2'(trimethylammonium) ethyl phosphate inner salt: butyl methacrylate (3:7) produced by an analogous procedure. The coating copolymer was dissolved in ethanol and a polyurethane membrane immersed in the solution for 1 minute and then dried at room temperature for 16 hours. The procedure was repeated twice and the membrane was then dried under reduced pressure at room temperature.

The surfaces of the coated membranes were analysed by x-ray photoelectron spectroscapy (XPS, Shimadzu ESCA-750, Kyoto). XPS analysis was also conducted on coated membranes which had been immersed in water, ethanol or 40% aqueous ethanol for 3 hours.

XPS analysis showed the presence of a phosphorous peak and nitrogen peaks attributable to the phosphate ester inner salt groups in the coating copolymer on the membrane's surface. These were shown to be retained upon immersion in water, ethanol or aqueous ethanol for the copolymers of Examples 4 to 6 to a significantly greater extent than on a membrane coated with the comparison copolymer with butylmethacrylate. These results are confirmed by the ratio of phosphorous to carbon obtained by XPS analysis for Pellethane membranes coated with copolymers of Examples 4 to 6 and the comparison copolymer (C), in the following table:

Example	No Immersion	H_2O Immersion	P/C Ratio EtOH Immersion	$EtOH/H_2O$ Immersion
4	0.036	0.035	0.026	0.029
5	0.023	0.022	0.019	0.022
6	0.037	0.028	0.028	0.030
C	0.034	0.023	0.016	0.018

These results indicate that copolymers of the invention which contain pendant polyurethane-like groups adhere to polyurethane substrates significantly more strongly than the comparison copolymers which do contain pendant zwitterionic and butyl groups but no pendant polyurethane-like groups.

EXAMPLE 8

Blood Contact Test

Disks (15 mm in diameter) of polyurethane membrane, produced by Example 7, were placed in a cell culture plate

and fixed in place with a silicone ring. The membrane surface was equilibrated using 1 ml of phosphate buffered saline (PBS) (PH 7.4, ionic strength 0.15 M) was added and incubated for 15 hours. The PBS was removed and 1 ml of rabbit citrated whole blood or platelet-rich plasma (PRP) was contacted with the membrane and maintained at 37°C for 60 minutes. The blood or RPR was then removed with a vacuum aspirator and the membrane rinsed three times with 1 ml of PBS. 1 ml of 2.5 vol% glutaraldehyde in PBS was added and maintained at room temperature for 2 hours to fix the blood component to the membrane. After rinsing with distilled water, the membranes were freeze-dried and the surfaces observed with scanning electron microscopy following gold spattering on the membrane surface.

Figure 2 shows scanning electronmicrographs of Pellethane membranes after contact with rabbit platelet-rich plasma for 60 minutes. (a) shows a membrane untreated with coating copolymer, (b) shows a membrane treated with a copolymer of (2(methacryloyloxy ethyl)-2'(trimethylammonium)ethyl phosphate inner salt): -butylmethacrylate (3:7) as a comparison, and (c), (d) and (e) show membranes coated with copolymers of the invention prepared in accordance with Examples 4, 5 and 6 respectively.

Figure 3 shows scanning electronmicrographs of polyurethane TM-3 membranes after contact with rabbit platelet-rich plasma for 60 minutes. (a) shows a membrane untreated with coating copolymer and (b), (c) and (d) show membranes coated with copolymers of the invention prepared in accordance with Examples 4, 5 and 6. The micrographs show a substantially greater deposit of platelets on the uncoated membranes (a) than those which have been coated with copolymers obtained by Examples 4 to 6, [Fig 2 (c)-(e) and Fig 3 (b)-(d)].

CLAIMS

1. A polymer of one or more radical polymerisable monomers, which polymer has pendant zwitterionic groups and other pendant groups containing an -NRC(O)NR- or -NRC(O)O- moiety, where the groups R are the same or different and each is hydrogen or alkyl of 1 to 4 carbon atoms, capable of stably binding the polymer by physisorption to a polymeric substrate surface or capable of providing compatibility with a base polymer in a blend.

2. A polymer according to claim 1 obtained by copolymerising a radical polymerisable, preferably an ethylenically unsaturated, comonomer containing a zwitterionic group and a radical polymerisable, preferably an ethylenically unsaturated, comonomer containing a radical polymerisable moiety and a group containing an -NRC(O)NR- or NRC(O)O- moiety.

3. A polymer according to claim 1 obtained by polymerising a radical polymerisable, preferably ethylenically unsaturated, monomer containing a zwitterionic group and a group containing an -NRC(O)NR- or -NRC(O)O- moiety.

4. A polymer according to any preceding claim comprising residues of one or more diluent comonomers and/or reactive comonomers to provide points of attachment for a ligand, or crosslinking.

5. A polymer according to any preceding claim in which the centre of permanent positive charge in the zwitterionic monomer is provided by a quaternary nitrogen atom and the centre of negative charge is provided by a phosphate group.

6. A polymer according to any preceding claim in which the zwitterionic monomer has the general formula (I)

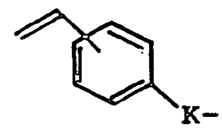
$$Y-B-X \qquad (I)$$

wherein B is a straight or branched alkylene, oxaalkylene or oligo-oxaalkylene chain optionally containing one or more fluorine atoms up to and including perfluorinated chains or, if X contains a carbon-carbon chain between B and the zwitterionic group or if Y contains a terminal carbon atom bonded to B, a valence bond;

X is a zwitterionic group and

Y is an ethylenically unsaturated polymerisable group selected from

$$CH_2{=}\underset{\displaystyle}{\overset{\displaystyle R^1}{\overset{|}{C}}}-\underset{\underset{\displaystyle O}{\|}}{C}-A- \quad \text{or}$$



wherein:

R^1 is hydrogen or a C_1-C_4 alkyl group;

A is -O- or $-NR^2-$ where R^2 is hydrogen or a C_1-C_4 alkyl group or R^2 is -B-X where B and X are as defined above; and

K is a group $-(CH_2)_pOC(O)-$, $-(CH_2)_pC(O)O-$, $-(CH_2)_pOC(O)O-$, $-(CH_2)_pNR^3-$, $-(CH_2)_pNR^3C(O)-$, $-(CH_2)_pC(O)NR^3-$, $-(CH_2)_pNR^3C(O)O-$, $-(CH_2)_pOC(O)NR^3-$, $-(CH_2)_pNR^3C(O)NR^3-$, (in which the groups R^3 are the same or different) $-(CH_2)_pO-$, $-(CH_2)_pSO_3$ -, or, optionally in combination with B, a valence bond and p is from 1 to 12 and R^3 is hydrogen or a C_1-C_4 alkyl group.

7. A polymer according to claim 6 in which the monomer has the formula

$$CH_2{=}\overset{\displaystyle R'}{\overset{|}{C}} - \overset{\displaystyle O}{\overset{\|}{C}} - O - B' - O - \underset{\underset{\displaystyle O^-}{|}}{\overset{\overset{\displaystyle O}{\|}}{P}} - O - (CH_2)_e\,\overset{+}{N}(R^7)_3$$

where R′ is hydrogen or methyl, B′ is alkylene having up to 12 carbon atoms, the groups R^7 are the same or different and each is hydrogen, C_{1-4} alkyl, aryl, such as phenyl, or two of the groups R^7, together with the nitrogen atom to which they are attached, form a heterocyclic ring containing from 5 to 7 atoms or the three groups R^7, together with the nitrogen atom to which they are attached, form a fused ring structure containing from 5 to 7 atoms in each ring and e is from 1 to 20.

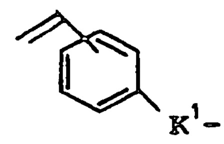
8. A polymer according to claim 7 in which R^7 are each hydrogen or C_{1-4}alkyl, preferably are all methyl.

9. A polymer according to any preceding claim, in which comonomers containing a polyurethane-like group are those of general formula (VI)

$$Y^1\text{-}Q \qquad \text{(VI)}$$

where Y^1 is an ethylenically unsaturated polymerisable group selected from

$$H_2C{=}\overset{\displaystyle R^{14}}{\overset{|}{C}}-\underset{\underset{\displaystyle O}{\|}}{C}-A'- \qquad \text{or}$$



where R^{14} is hydrogen or C_1-C_4 alkyl,

A' is -O- or $-NR^{15}-$ where R^{15} is hydrogen or a C_1-C_4 alkyl group or R^{15} is a group Q;

K^1 is a group $-(CH_2)_lOC(O)-$, $-(CH)_lC(O)O-$, $-(CH_2)_lOC(O)O-$, $-(CH_2)_lNR^{16}-$, $-(CH_2)_lNR^{16}C(O)-$, $-(CH_2)_lC(O)NR^{16}-$, $-(CH_2)_lNR^{16}C(O)O-$, $-(CH_2)_lOC(O)NR^{16}-$, $-(CH_2)_lNR^{16}C(O)NR^{16}-$ (in which the groups R^{16} are the same or different), $-(CH_2)_lO-$, $-(CH_2)_lSO_3-$, a valence bond and l is from 1 to 12 and R^{16} is hydrogen or a C_1-C_4 alkyl group; and

Q is a group containing an -NRC(O)NR- or -NRC(O)- moiety capable of said stable binding or compatibility.

10. A polymer according to claim 9 in which the monomer has the formula

$$CH_2{=}\overset{\displaystyle R^{14}}{\overset{|}{C}} - \overset{\displaystyle O}{\overset{\|}{C}} - O - Q$$

where Q is a group of formula (IXA) or (IXB)

$$-R^{17}-NRC(O)NR-R^{18} \qquad \text{(IXA)}$$

$$-R^{17}-NRC(O)O-R^{18} \qquad \text{(IXB)}$$

wherein R, (or the two groups R in (IXA), which may be the same or different each) is hydrogen or C_{1-4} alkyl;

R^{17} is alkylene, arylene, alkylarylene, arylalkylene or alkylarylalkylene, cycloalkylene, alkylcycloalkylene, cycloalkyl-alkylene or alkyl-cycloalkyl-alkylene; and

R^{18} is alkyl, aryl or alkylaryl or cycloalkyl or alkylcycloalkyl wherein the alkyl groups may optionally be interrupted by one or more arylene or cycloalkylene groups, and wherein R^{18} may optionally contain one or more groups

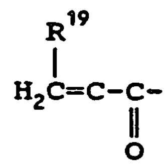
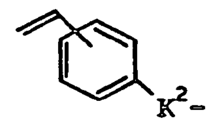
-NRC(O)NR- or -NRC(O)O- as hereinbefore defined.

11. A polymer according to claim 10 in which R is hydrogen, methyl or ethyl, preferably hydrogen.

12. A polymer according to any preceding claim comprising residues of a comonomer bearing a reactive group of the general formula (XI)

$$Y^2\text{-}Q^1 \qquad \text{(XI)}$$

where Y^2 is an ethylenically unsaturated polymerisable group selected from

 or 

where R^{19} is hydrogen or C_1-C_4 alkyl,

K^2 is a group $-(CH_2)_qOC(O)-$, $-(CH)_qC(O)O-$, $-(CH_2)_qOC(O)O-$, $-(CH_2)_qNR^{20}-$, $-(CH_2)_qNR^{20}C(O)-$, $-(CH_2)_qC(O)NR^{20}-$, $-(CH_2)_qNR^{20}C(O)O-$, $-(CH_2)_qOC(O)NR^{20}-$, $-(CH_2)_qNR^{20}C(O)NR^{20}-$ (in which the groups R^{20} are the same or different), $-(CH_2)_qO-$, or $-(CH_2)_qSO_3-$, or a valence bond and q is from 1 to 12 and R^{20} is hydrogen or a C_1-C_4 alkyl group; and

Q^1 is a reactive group capable of reacting to provide covalent bonding, or crosslinking, selected from groups containing cinnamyl, epoxy, $-CHOHCH_2Hal$ (in which Hal is a halogen atom), methylol or silyl group, an ethylenically unsaturated crosslinkable group such as an acetylenic, diacetylenic, vinylic or divinylic group, an acetoacetoxy group or chloroalkyl sulfone, preferably chloroethyl sulphone, group or a hydroxyl, amino or carboxylic acid group or an activated derivative thereof such as a succinimido, tosylate, triflate, imidazole carbonyl-amino or substituted triazine group.

13. A process for preparing a polymer according to claim 2 copolymerising a comonomer containing a zwitterionic group and a comonomer containing a polyurethane-like group, optionally with a diluent and/or reactive comonomer.

14. A process for preparing a polymer according to claim 3 polymerising a monomer containing a zwitterionic group

and a polyurethane-group, optionally with a diluent and/or a reactive comonomer.

15. A process according to claim 13 or 14 comprising 5 to 75% by mole, residues of a diluent monomer and/or 0.1 to 20%, by mole, of a reactive comonomer.

16. A product comprising a polymeric substrate coated with or a base polymer blended with a polymer according to any of claims 1 to 12.

17. A product according to claim 16 in which the polymeric substrate or base polymer is a polyurethane.

18. A product according to claim 16 or 17 which is a device to be contacted with blood or protein or microorganisms.

19. A process for biocompatibilising a polymeric substrate by coating its surface with a polymer according to any of claims 1 to 12.

20. A process according to claim 19 in which the polymeric substrate comprises a polyurethane.

21. A process according to claim 19 or 20 in which the platelet activation of the surface of the substrate is reduced by at least 70% by the coating.

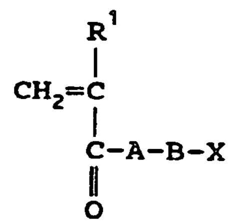
22. A process according to any of claims 19 to 21 in which the fibrinogen absorption of the surface of the substrate is reduced by at least 60% by the coating.

23. A process in which a base polymer and a polymer according to any of claims 1 to 12 are blended together.

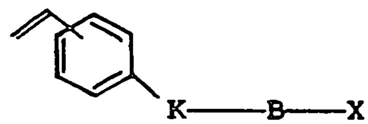
24. A process according to claim 23 in which the base polymer is a polyurethane.

25. A process according to claim 23 or 24 in which the blend is shaped to form an article.

26. A compound of the formula



(II)



(III)

wherein B is a straight or branched alkylene, oxaalkylene or oligo-oxaalkylene chain optionally containing one or more fluorine atoms up to and including perfluorinated chains or, if X contains a carbon-carbon chain between B and the zwitterionic group or if Y contains a terminal carbon atom bonded to B, a valence bond;

R^1 is hydrogen or a C_1-C_4 alkyl group;

A is -O- or $-NR^2-$ where R^2 is hydrogen or a C_1-C_4 alkyl group or R^2 is -B-X where B is as defined above; and K is a group $-(CH_2)_pOC(O)-$, $-(CH_2)_pC(O)O-$, $-(CH_2)_pOC(O)O-$, $-(CH_2)_pNR^3-$, $-(CH_2)_pNR^3C(O)-$, $-(CH_2)_pC(O)NR^3-$, $-(CH_2)_pNR^3C(O)O-$, $-(CH_2)_pOC(O)NR^3-$, $-(CH_2)_pNR^3C(O)NR^3-$, (in which the groups R^3 are the same or different) $-(CH_2)_pO-$, $-(CH_2)_pSO_3-$, or, optionally in combination with B, a valence bond and p is from 1 to 12 and R^3 is hydrogen or a C_1-C_4 alkyl group, and X is selected from groups VA, VB and VC;

```
                 O
                 ‖
        CH2-O-P-O-(CH2)i-+N(R11)3        (VA)
        |        |
-[O]z-CH         O-
        |
        CH2-O-R11a
```

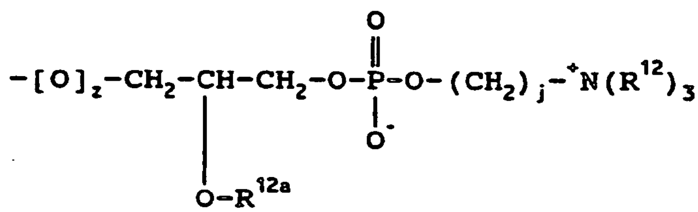
wherein the groups R^{11} are the same or different and each is hydrogen, C_{1-4} alkyl, aryl, such as phenyl, or two of the groups R^{11}, together with the nitrogen atom to which they are attached, form a heterocyclic ring containing from 5 to 7 atoms or the three groups R^{11}, together with the nitrogen atom to which they are attached, form a fused ring structure containing from 5 to 7 atoms in each ring,

R^{11a} is a group of formula $-C(O)R^{11b}$, in which R^{11b} is a group containing an -NRC(O)NR- or -NRC(O)O- moiety capable

of stably binding to a polymeric substrate surface by physisorption,

i is from 1 to 20; and

if B is other than a valence bond z is 1 and if B is a valence bond z is 0 if X is directly bonded to an oxygen or nitrogen atom and otherwise z is 1;



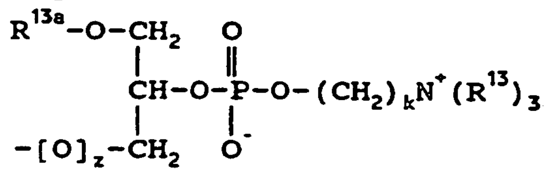
(VB)

wherein the groups R^{12} are the same or different and each is hydrogen, C_1-C_4 alkyl, aryl such as phenyl, or two of the groups R^{12}, together with the nitrogen atom to which they are attached, form a heterocyclic ring containing from 5 to 7 atoms or the three groups R^{12}, together with the nitrogen atom to which they are attached, form a fused ring structure containing from 5 to 7 atoms in each ring,

R^{12a} is a group of formula $-C(O)R^{12b}$, in which R^{12b} is a group containing an -NRC(O)NR- or -NRC(O)- moiety capable of stably binding to a polyurethane substrate surface by physisorption;

j is from 1 to 20; and

if B is other than a valence bond, z is 1 and if B is a valence bond z is 0 if X is directly bonded to an oxygen or nitrogen atom and otherwise z is 1;



(VC)

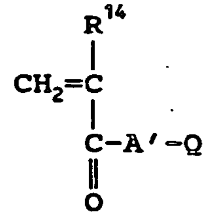
wherein the groups R^{13} are the same or different and each is hydrogen, $_{1-4}$ alkyl, aryl, such as phenyl, or two of the groups R^{13}, together with the nitrogen atom to which they are attached, form a heterocyclic ring containing from 5 to 7 atoms or the three groups R^{13}, together with the nitrogen atom to which they are attached, form a fused ring structure containing from 5 to 7 atoms in each ring,

R^{13a} is a group of formula $-C(O)R^{13b}$, in which R^{13a} is a group containing an -NRC(O)NR- or -NRC(O)- moiety capable of stably binding to a polyurethane substrate surface by physisorption;

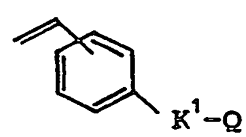
k is from 1 to 20; and

if B is other than a valence bond, z is 1 and if B is a valence bond z is 0 if X is directly bonded to an oxygen or nitrogen atom and otherwise z is 1; or analogues of any of the groups VA, VB, or VC in which in which the quaternary ammonium group NR_3' is replaced by a phosphonium group $-^{+}PR'_r(OR')_{3-r}$ where r is from 0 to 3, or a sulphonium group $-^{+}SR'_2$, where R' corresponds to R^{11}, R^{12}, or R^{13} or a group Het^{+}, where Het is a nitrogen, phosphorous or sulphur-containing heterocycle, such as a pyridinium group.

27. A compound of the formula VII or VIII



(VII)



(VIII)

in which R^{14} is hydrogen or C_1-C_4 alkyl,

A' is -O- or $-NR^{15}-$ where R^{15} is hydrogen or a C_1-C_4 alkyl group or R^{15} is a group Q;

K^1 is a group $-(CH_2)_lOC(O)-$, $-(CH)_lC(O)O-$, $-(CH_2)_lOC(O)O-$, $-(CH_2)_lNR^{16}-$, $-(CH_2)_lNR^{16}C(O)-$, $-(CH_2)_lC(O)NR^{16}-$, $-(CH_2)_lNR^{16}C(O)O-$, $-(CH_2)_lOC(O)NR^{16}-$, $-(CH_2)_lNR^{16}C(O)NR^{16}-$ (in which the groups R^{16} are the same or different), $-(CH_2)_lO-$, $-(CH_2)_lSO_3-$, a valence bond and l is from 1 to 12 and R^{16} is hydrogen or a C_1-C_4 alkyl group; and

Q is a group of formula (IXA) or (IXB)

$$-R^{17}-NRC(O)NR-R^{18} \qquad (IXA)$$

$$-R^{17}-NRC(O)O-R^{18} \qquad (IXB)$$

wherein R, (or the two groups R in (IXA), which may be the same or different each) is hydrogen or C_{1-4} alkyl;

R^{17} is alkylene, arylene, alkylarylene, arylalkylene or alkylarylalkylene, cycloalkylene, alkylcycloalkylene, cycloalkyl-alkylene or alkyl-cycloalkyl-alkylene; and

R^{18} is alkyl, aryl or alkylaryl or cycloalkyl or alkylcycloalkyl wherein the alkyl groups may optionally be interrupted by one or more arylene or cycloalkylene groups, and wherein R^{18} may optionally contain one or more groups

-NRC(O)NR- or -NRC(O)O- as hereinbefore defined.

28. A compound according to claim 28 selected from
phenylaminocarbonylaminophenylmethylphenylamino-carbonylaminoethyl methacrylate;
cyclohexylaminocarbonylaminocyclohexylmethyl-cyclohexylaminocarbonylaminoethyl methacrylate;
butyloxycarbonylaminoethyl methacrylate;
benzyloxycarbonylaminoethyl methacrylate;
phenyloxycarbonylaminoethyl methacrylate; and
cyclohexyloxycarbonylaminoethyl methacylate.

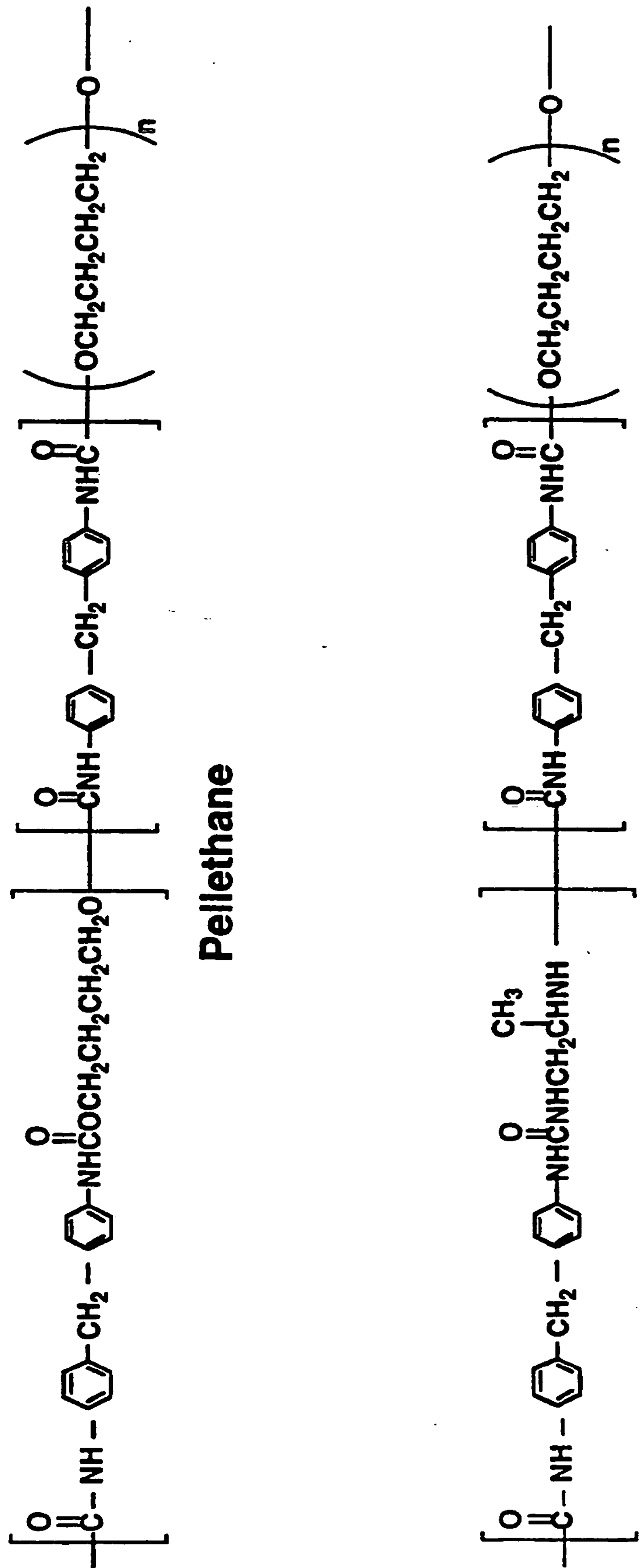
29. A process for producing a compound according to claim 27 which comprises reacting a corresponding compound containing, in place of the group of formula (IXA) or (IXB), a group of formula (X)

$$-R^{17}-NCO \quad (X)$$

where R^{17} is as hereinbefore defined in claim 27 with

(a) a compound $R^{18}-NH_2$ or an activated derivative thereof where R^{18} is as defined in claim 27 to produce a compound containing a group of formula (IXA); or

(b) a compound $R^{18}-OH$, or an activated derivative thereof where R^{18} is as defined in claim 27 to produce a compound containing a group of formula (IXB).



Pellethane

TM-3

FIGURE 1

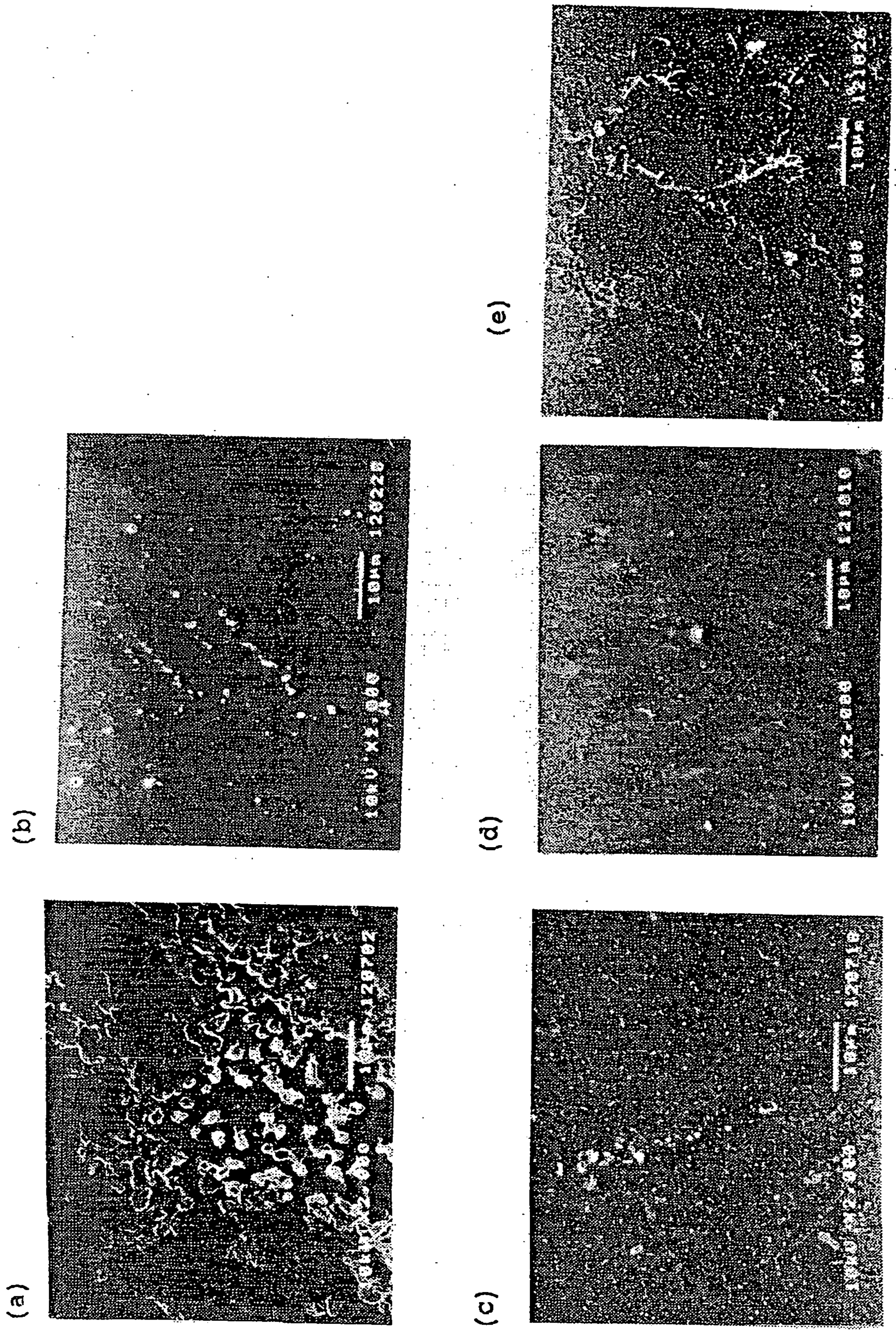


FIGURE 2

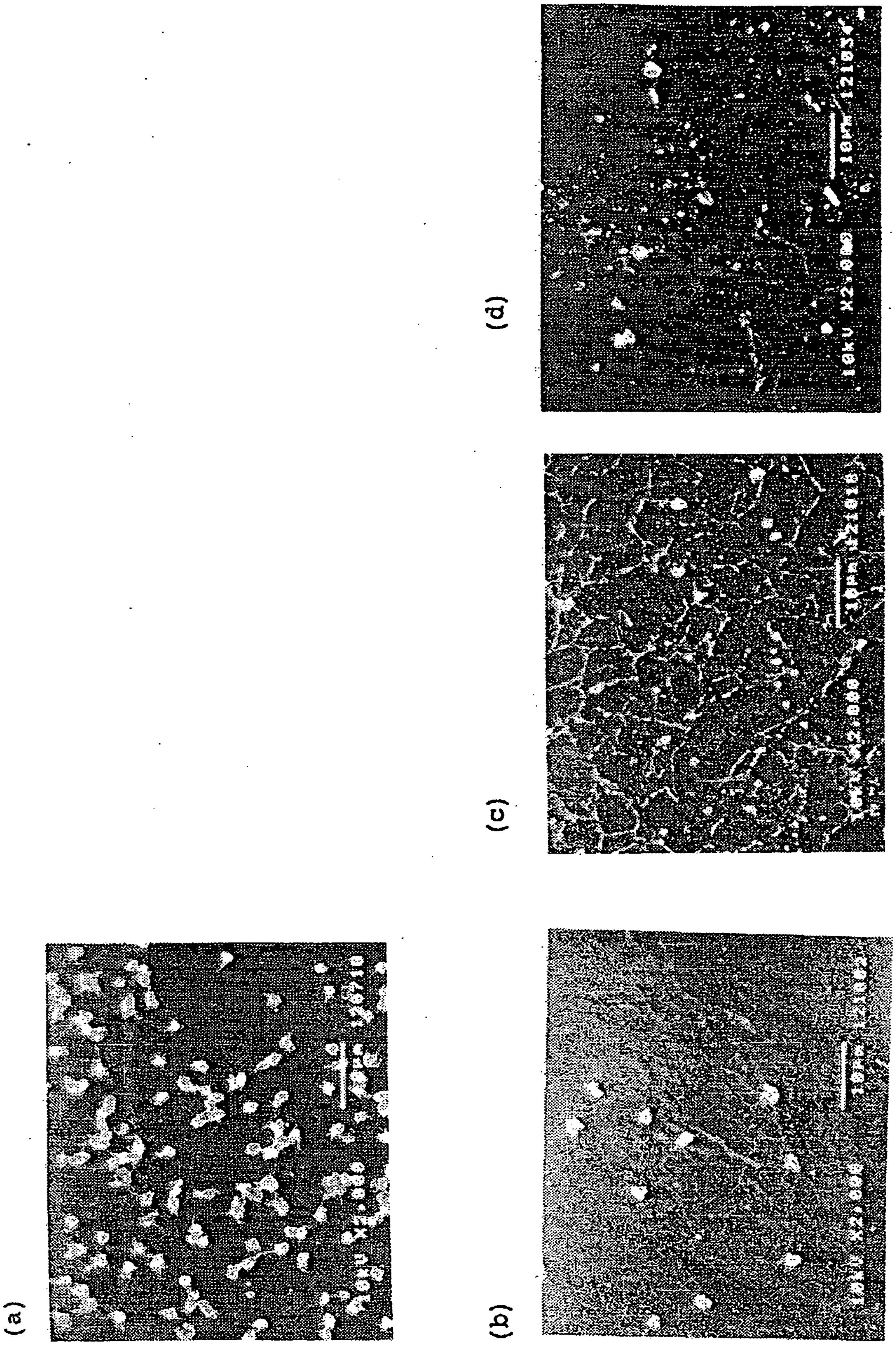


FIGURE 3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 94/01805

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C08F246/00 C07F9/09 C09D157/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C08F C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,93 01221 (BIOCOMPATIBLES LTD.) 21 January 1993 cited in the application -----	

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
15 November 1994	- 1. 12. 94

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 94/01805

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9301221	21-01-93	AU-A- 2231092	11-02-93
		CA-A- 2112411	21-01-93
		EP-A- 0593561	27-04-94